Physiologists are studying the biomolecular mechanisms underlying skeletal muscle contraction. They have been analyzing muscle fibers obtained from knockout mice to determine how different cellular substances influence muscular contraction. Striated muscle fibers obtained from a specific mouse embryo fail to contract in response to a substance normally released from the sarcoplasmic reticulum. A deficiency of which of the following would best explain this finding?

A. Acetylcholine

B. Epinephrine

C. Calmodulin

D. Myosin light-chain kinase

E. Troponin

Submit

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A. Acetylcholine (4%)

B. Epinephrine (0%)

C. Calmodulin (18%)

D. Myosin light-chain kinase (9%)

✓ E. Troponin (67%)

Omitted
Correct answer
E

67%
Answered correctly

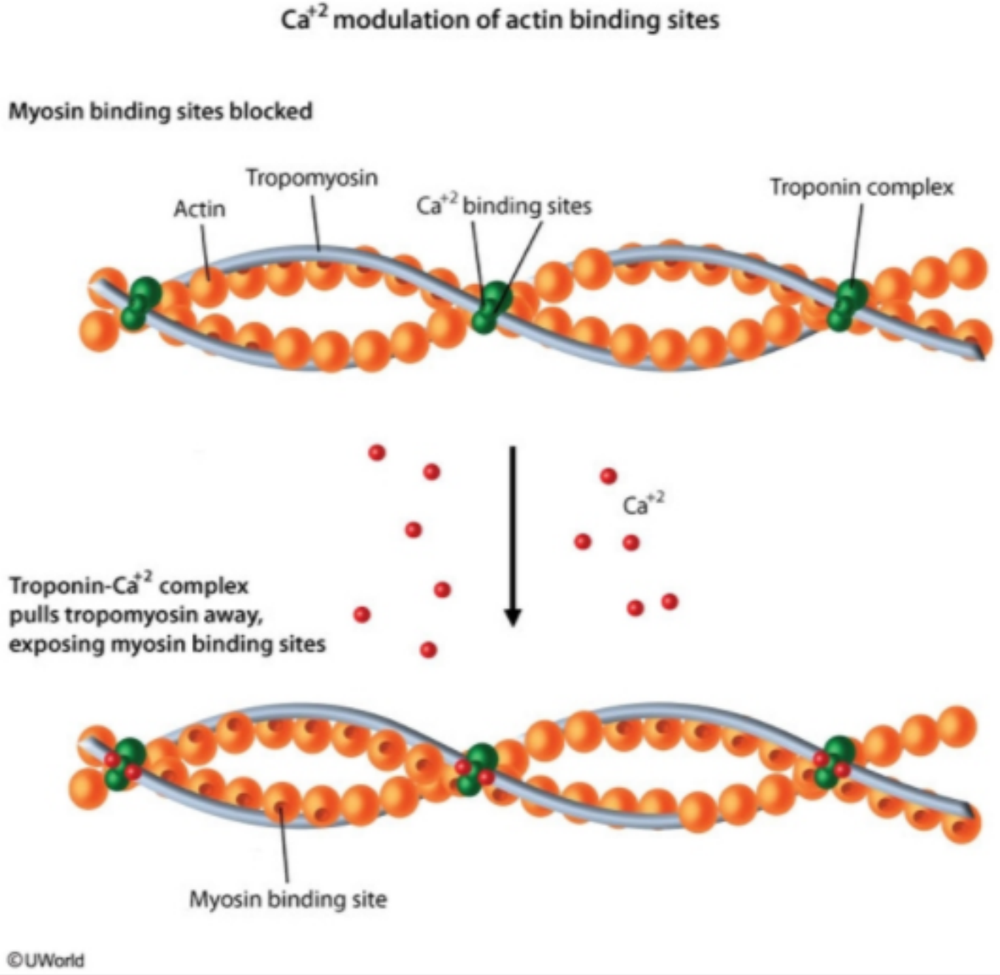
14 secs
Time Spent

07/04/2020
Last Updated

Explanation

Explanation

Exhibit Display



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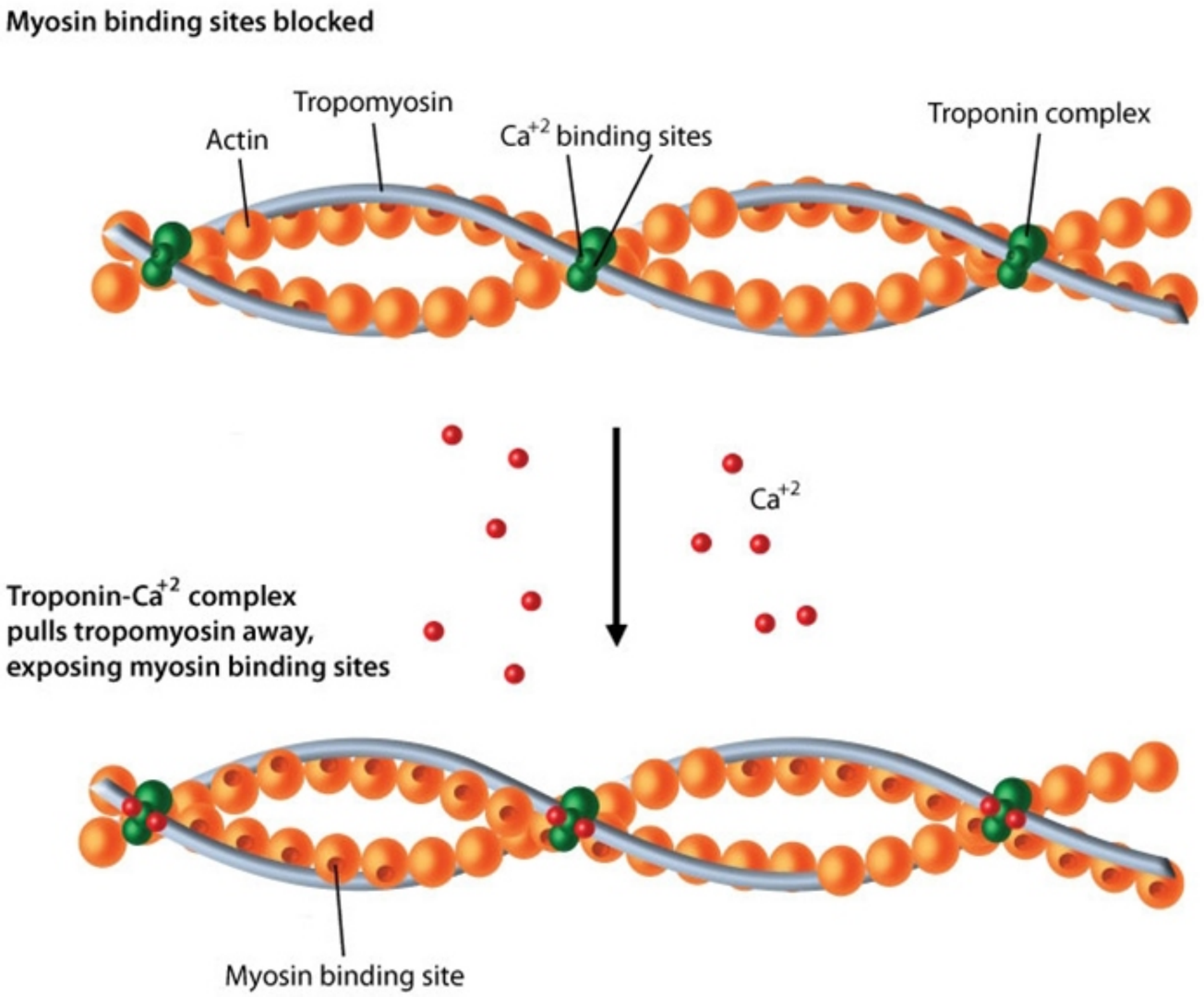
Ca^{+2} modulation of actin binding sites



The contractile mechanism in skeletal muscle depends on proteins (myosin II, actin, tropomyosin, and troponin) as well as calcium ions. The thick filaments in skeletal muscle are comprised of myosin molecules, with the heads of the myosin molecules forming cross-links with actin during muscular contraction. Two actin chains comprise the thin filaments in skeletal muscle. Tropomyosin molecules sit in the groove between the two actin chains, covering the myosin binding sites on actin when the muscle is at rest. Troponin molecules are small globular proteins situated alongside the tropomyosin molecules. Troponin is composed of three subunits: troponin T, troponin I, and troponin C. Troponin T binds the other troponin components to tropomyosin, troponin I binds the troponin-tropomyosin complex to actin, and troponin C contains the binding sites for Ca^{2+}. During excitation-contraction coupling, Ca^{2+} is released from the sarcoplasmic reticulum. When Ca^{2+} binds troponin C, tropomyosin shifts to expose the actin binding sites for myosin, allowing contraction to occur.

(Choice A) Acetylcholine is the neurotransmitter that initiates muscle contraction in response to motor neuron stimulation. Acetylcholine release from the motor neuron opens post-synaptic ligand-gated ion channels, resulting in depolarization of the muscle cell. Depolarization then causes release of Ca^{2+} from the sarcoplasmic reticulum.

(Choice B) Epinephrine is a catecholamine that is not directly involved in skeletal muscle contraction. However, epinephrine stimulates β2-adrenergic receptors to increase skeletal muscle blood flow, glycogenolysis, and lipolysis.

(Choices C and D) Calmodulin and myosin light-chain kinase are elements of the contractile mechanism in smooth muscle, not skeletal muscle.

Educational objective:
The contractile mechanism in skeletal muscle depends on proteins (myosin II, actin, tropomyosin, and troponin) as well as calcium ions.

Physiology	Rheumatology/Orthopedics & Sports	Muscle structure & physiology
Subject	System	Topic

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A 67-year-old man comes to the office with right tibial pain that started 3 months ago and has increased in intensity over time. He also has had progressive hearing impairment for the last year. Physical examination reveals local tenderness and a lumpy protuberance over the right tibia. After extensive evaluation, the patient undergoes a bone biopsy. The pathologist identifies numerous multinucleated cells, some containing over 100 nuclei. Which of the following factors is essential for the differentiation of the cells described by the pathologist?

A. Fibroblast growth factor

B. Insulin-like growth factors

C. Osteoprotegerin

D. Receptor activator of nuclear factor kappa-B ligand

E. Transforming growth factor beta

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- A. Fibroblast growth factor (13%)
- B. Insulin-like growth factors (4%)
- C. Osteoprotegerin (14%)
- ✓ D. Receptor activator of nuclear factor kappa-B ligand (52%)
- E. Transforming growth factor beta (13%)

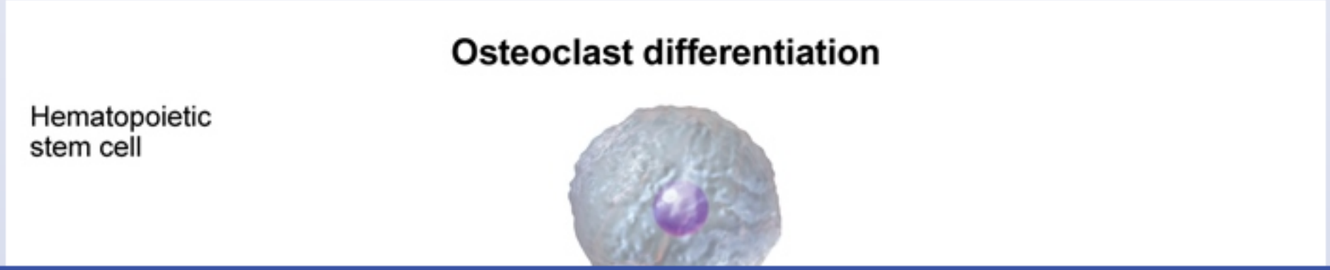
Omitted
Correct answer
D

52%
Answered correctly

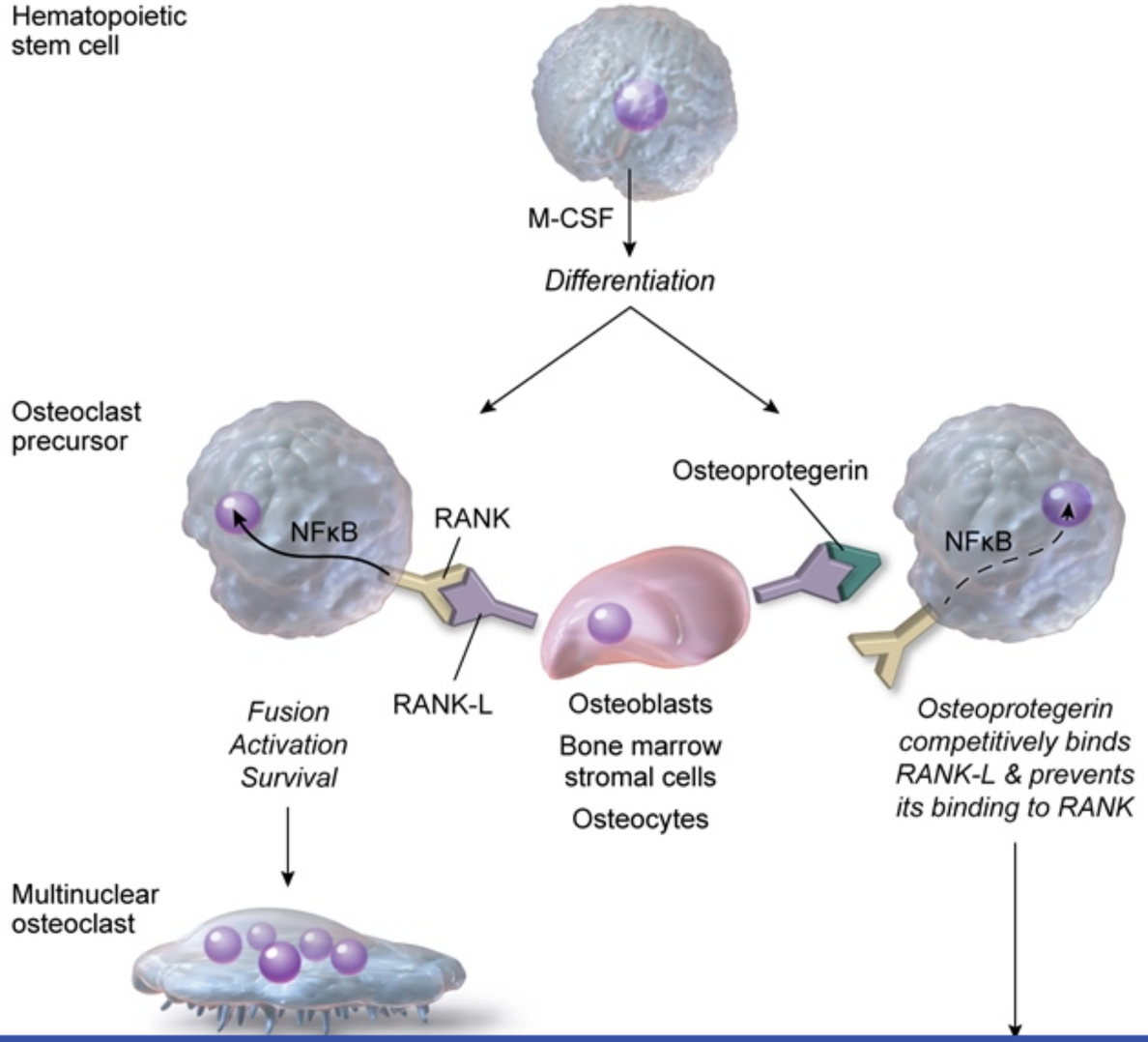
02 secs
Time Spent

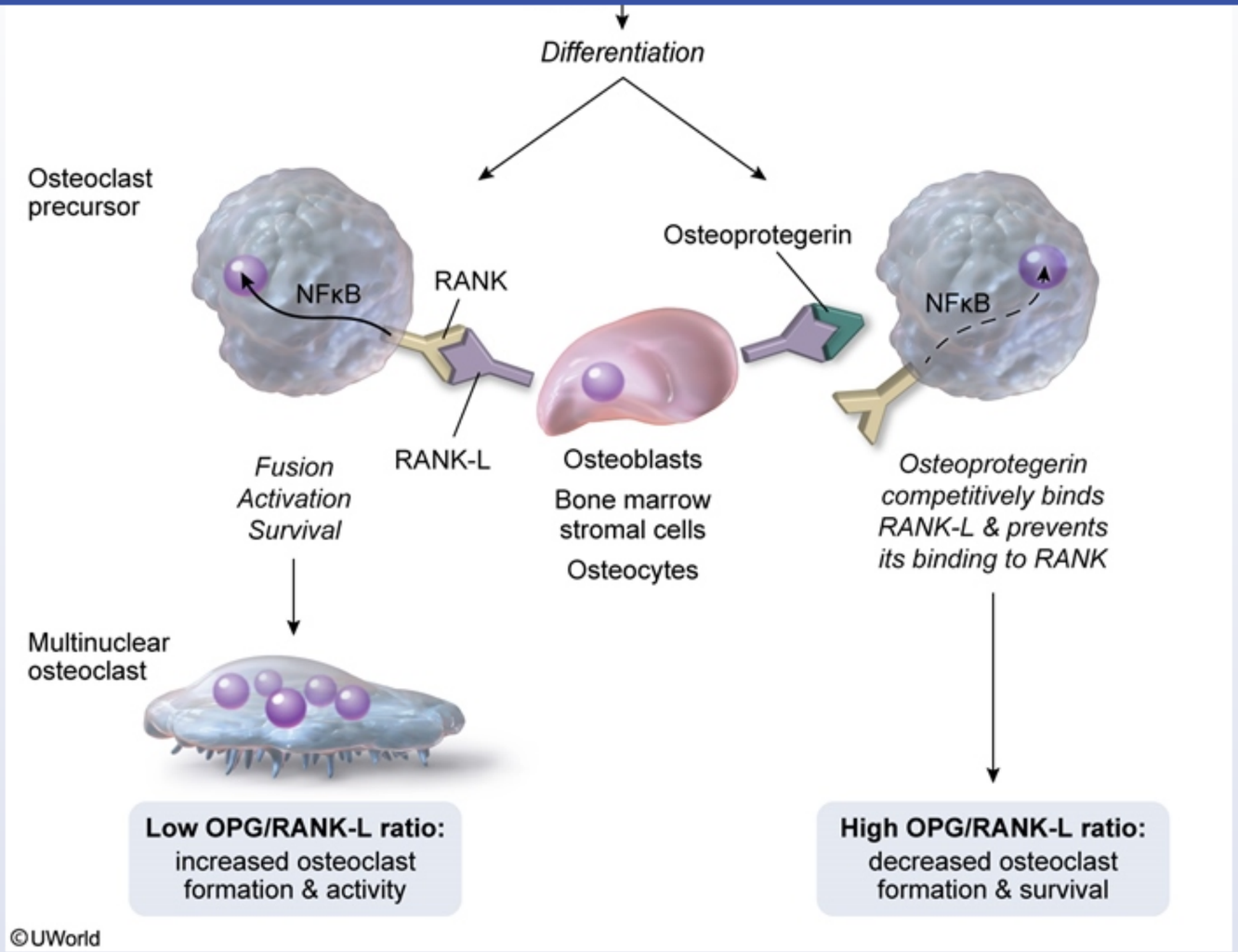
03/11/2020
Last Updated

Explanation



Osteoclast differentiation





This patient has pain and deformity of the long bones with hearing loss (due to bony deformity of the skull); these are typical features of Paget's disease of bone. The initial abnormality in Paget's disease is excessive osteoclastic bone resorption followed by increased bone formation by osteoblasts; this results in **high bone turnover** in the affected areas. The new bone formation is disorganized, and pagetic bone lesions typically appear on imaging as thickened areas of mixed sclerosis and lucency.

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Osteoblasts are cells with a single nucleus that arise from mesenchymal stem cells found in the periosteum and bone marrow. In contrast, **osteoclasts** originate from the mononuclear phagocytic cell lineage and are ultimately formed when several precursor cells fuse to create a **multinucleated** mature cell. Osteoclasts in Paget's disease are typically very large and can have up to 100 nuclei (normal osteoclasts have 2-5). The 2 most important factors for osteoclastic differentiation, macrophage colony-stimulating factor (**M-CSF**) and receptor for activated nuclear factor kappa-B ligand (**RANK-L**), are produced by osteoblasts and bone marrow stromal cells.

Osteoprotegerin (OPG) is a physiologic decoy receptor that decreases binding of RANK-L to RANK. Inhibition of RANK-L to RANK receptor interaction reduces the differentiation and survival of osteoclasts, resulting in decreased bone resorption and increased bone density **(Choice C)**. OPG loss-of-function mutations cause juvenile Paget's disease. A monoclonal antibody (denosumab) that inhibits the RANK/RANK-L interaction also leads to increased bone density and is commonly used for the treatment of osteoporosis.

(Choice A) Fibroblast growth factors (FGFs) regulate chondrogenesis and osteogenesis. FGFs induce proliferation of osteoblastic precursor cells and anabolic function of mature osteoblasts. Abnormalities in the FGF receptor result in the congenital short-limbed dwarfism known as achondroplasia.

(Choice B) Insulin-like growth factors (IGF-I and IGF-II) are synthesized by various tissues, including the liver and bone. IGF-I increases osteoblastic replication and collagen synthesis; it also decreases collagen degradation by inhibiting the enzyme matrix metalloproteinase-13 (MMP-13). The net effect of IGF-I on the bone is anabolic.

(Choice E) Transforming growth factor beta increases the replication of osteoblast precursors, leading to increased formation of mature osteoblasts. Transforming growth factor beta also increases collagen synthesis and decreases bone resorption by increasing osteoclastic apoptosis.

Educational objective:
Osteoclasts originate from hematopoietic progenitor cells. Macrophage colony-stimulating factor and receptor for activated nuclear factor kappa-B

factor kappa-B ligand (**RANK-L**), are produced by osteoblasts and bone marrow stromal cells.

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Educational objective:
Osteoclasts originate from hematopoietic progenitor cells. Macrophage colony-stimulating factor and receptor for activated nuclear factor kappa-B ligand (RANK-L) play an important role in osteoclast differentiation. Paget's disease of bone is characterized by increased numbers of abnormal osteoclasts, excessive bone turnover and disorganized bone remodeling.

References

- Regulation of NFATc1 in osteoclast differentiation.

Physiology	Rheumatology/Orthopedics & Sports	Pagets disease of bone
Subject	System	Topic

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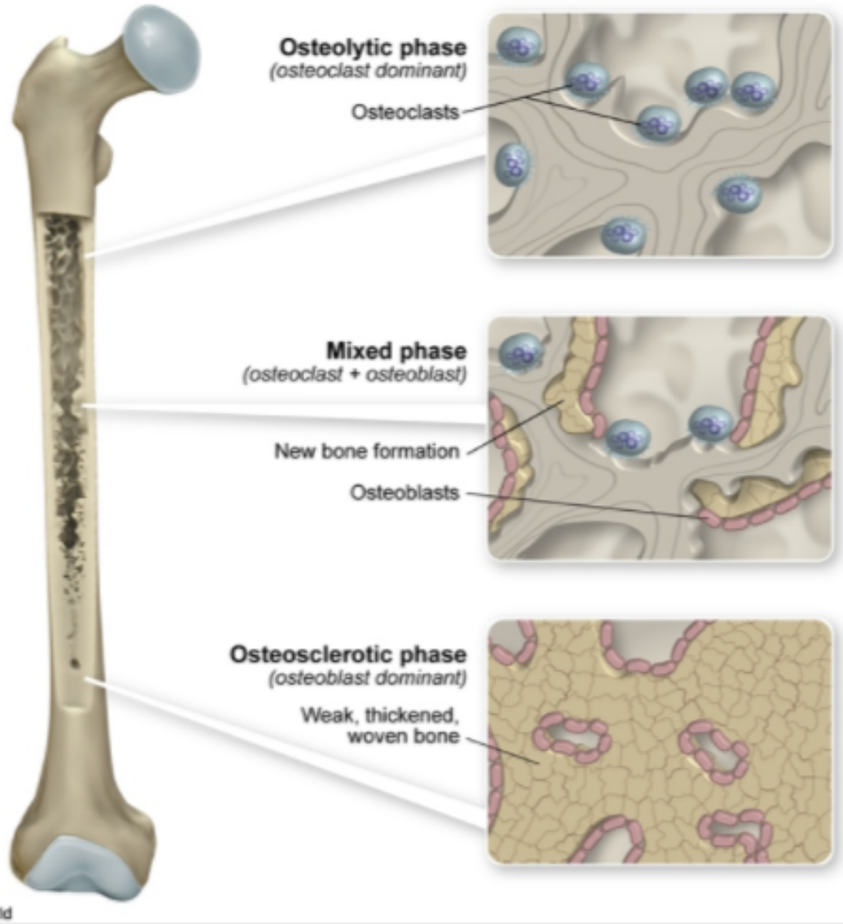
Multinuclear

Exhibit Display

Paget disease of bone



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Researchers are studying treatment of osteoporotic fractures. Subjects with pelvic fractures due to osteoporosis are divided into 2 groups. The control group receives physical therapy along with calcium and vitamin D supplementation. The experimental group receives a parathyroid hormone analogue in addition to the standard therapy. It is found that the subjects who receive hormonal treatment have a shorter time to fracture healing and improved functional outcome. The benefits of the investigational medication are attributed to increased osteoblastic activity. An elevated level of which of the following markers is most likely to reflect the medication effect in these subjects?

A. Serum alkaline phosphatase

B. Serum aspartate aminotransferase

C. Serum calcitonin

D. Serum tartrate-resistant acid phosphatase

E. Urinary hydroxyproline

F. Urinary type I collagen telopeptide

Submit

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- ✓ A. Serum alkaline phosphatase (72%)
- B. Serum aspartate aminotransferase (0%)
- C. Serum calcitonin (14%)
- D. Serum tartrate-resistant acid phosphatase (4%)
- E. Urinary hydroxyproline (3%)
- F. Urinary type I collagen telopeptide (4%)

Omitted
Correct answer
A

72%
Answered correctly

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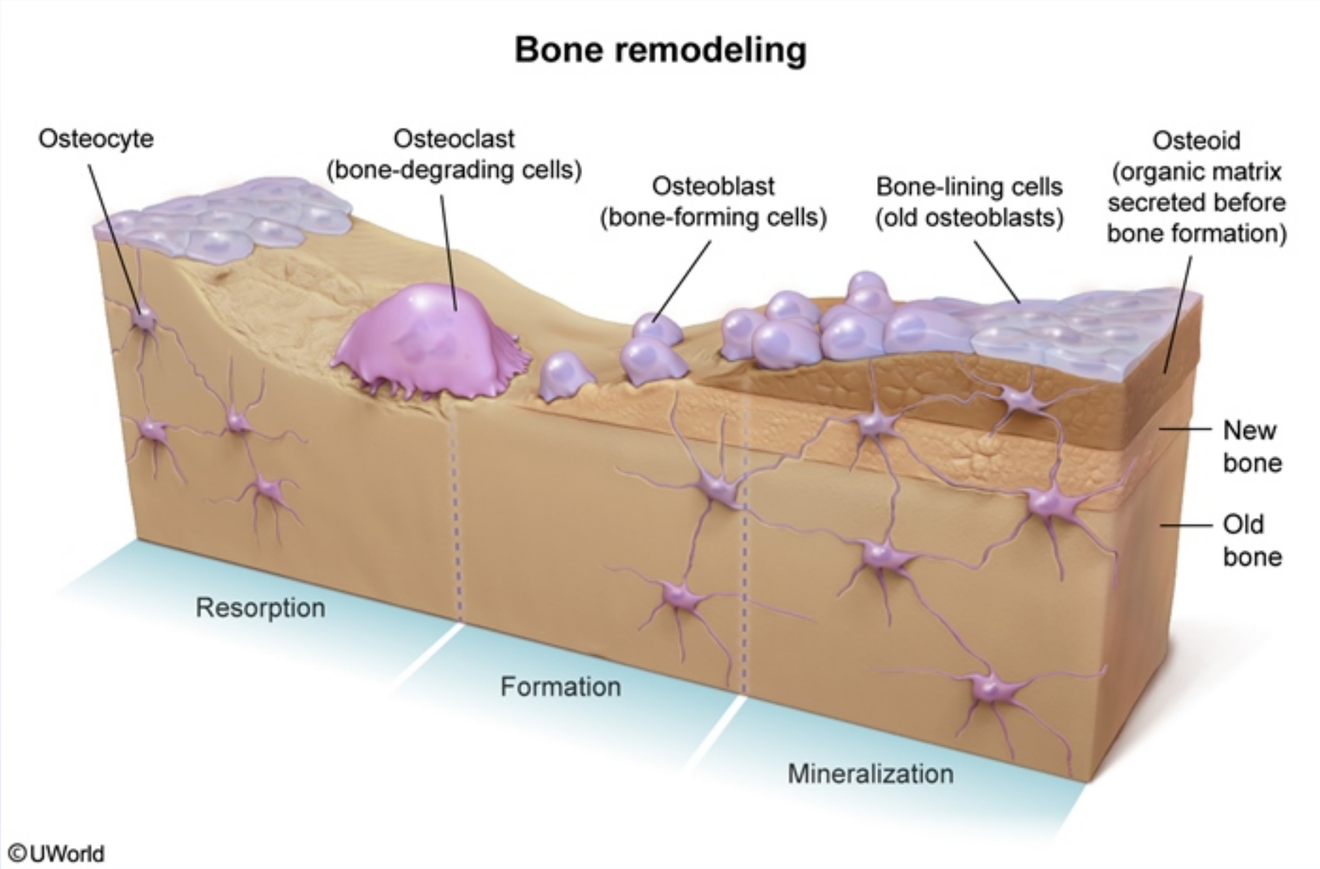
Time Spent

02/01/2020
Last Updated

Explanation

Bone remodeling

Osteocyte Osteoclast Osteoid



Bone is continually broken down and reformed by the process known as bone remodeling, which consists of the coordinated activity of osteoblasts (responsible for bone formation) and osteoclasts (responsible for bone resorption). The subjects in this study are receiving a **recombinant parathyroid hormone** analog (eg, teriparatide), which promotes **bone formation** by stimulating maturation of pre-osteoblasts into osteoblasts.

Osteoblasts synthesize bone matrix and express **alkaline phosphatase** (AlkP), which promotes normal bone mineralization by increasing local concentrations of inorganic phosphorus. Serum AlkP levels correlate with **osteoblastic activity**. However, total serum levels are nonspecific, as

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Osteoblasts synthesize bone matrix and express **alkaline phosphatase** (AlkP), which promotes normal bone mineralization by increasing local concentrations of inorganic phosphorus. Serum AlkP levels correlate with **osteoblastic activity**. However, total serum levels are nonspecific, as AlkP is also produced by the hepatobiliary tree, intestine, and placenta and may be elevated due to other causes (eg, pregnancy, biliary obstruction). If the source of AlkP is uncertain, AlkP isoenzymes (ie, liver, placental, intestinal, bone) can be differentiated with additional laboratory techniques (eg, electrophoresis, immunoassay). Other markers of osteoblast activity include **N-terminal propeptide of type 1 procollagen** (PINP), which is released during post-translation cleavage of type 1 procollagen before its assembly into mature type 1 collagen fibrils.

(Choice B) Aspartate aminotransferase (AST) is predominantly found in liver, muscle, and kidneys. AST is commonly used as a marker for hepatic injury and is also elevated in rhabdomyolysis and myocardial infarction.

(Choice C) Calcitonin is secreted by the parafollicular C cells of the thyroid and inhibits bone resorption by osteoclasts. As a laboratory marker, calcitonin is primarily used in the diagnosis of medullary thyroid cancer; it does not mark osteoblastic activity.

(Choice D) Acid phosphatase is a family of lysosomal enzymes present in a wide variety of cells, including osteoclasts (the acid phosphatase in osteoclasts is resistant to degradation by tartrate). However, osteoblasts do not express acid phosphatase.

(Choices E and F) Osteoclastic activity (ie, bone resorption) leads to breakdown of fibrillar collagen with release of biomarkers such as hydroxyproline and collagen telopeptides. Increased urine levels are associated with states of increased bone resorption (rather than formation).

Educational objective:
Bone-specific alkaline phosphatase levels correlate with osteoblast activity. Other markers of osteoblast activity include N-terminal propeptide of type 1 procollagen, which is released during post-translation cleavage of type 1 procollagen.

References

- International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis

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- International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis.
- Teriparatide increases the maturation of circulating osteoblast precursors.

Physiology	Rheumatology/Orthopedics & Sports	Bone remodeling
Subject	System	Topic

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A 42-year-old weightlifter is preparing for an upcoming strength competition. After lifting a series of progressively heavier weights, he decides to increase the weight on the exercise bar to 175 kg (385 lbs), the heaviest lift he has ever attempted. He is able to hold the weight over his head for several seconds. However, his arms suddenly and involuntarily give way and he drops the weight to the ground. Which of the following structures was most likely responsible for the sudden muscle relaxation?

A. A-delta nerve endings

B. Golgi tendon organ

C. Intrafusal muscle fibers

D. Pacinian corpuscles

E. Ruffini's end organs

Submit

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A. A-delta nerve endings (4%)
✓ B. Golgi tendon organ (71%)
C. Intrafusal muscle fibers (18%)
D. Pacinian corpuscles (3%)
E. Ruffini's end organs (1%)

Omitted
Correct answer
B

71%
Answered correctly

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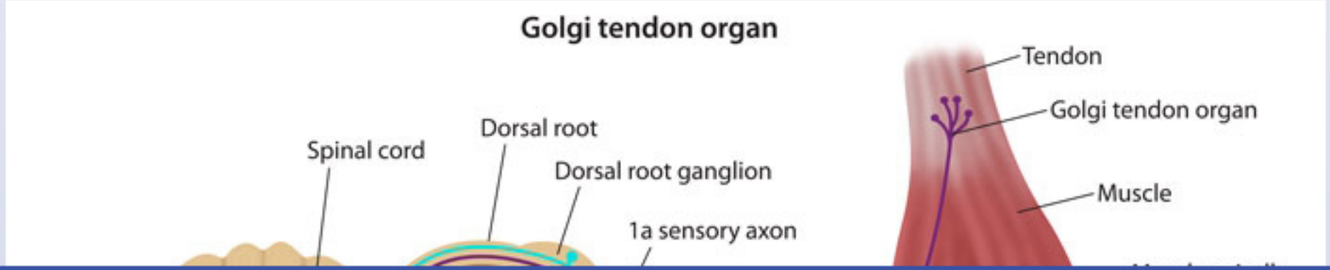
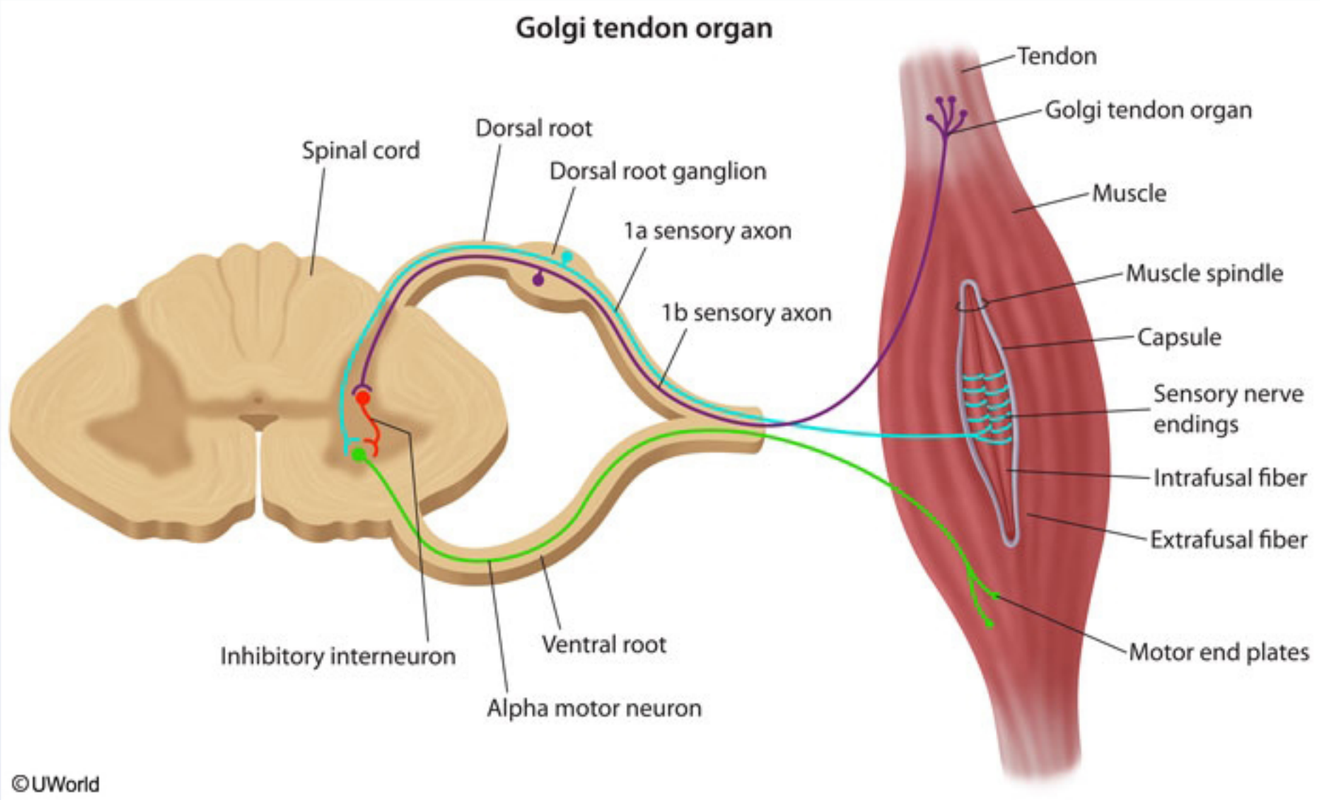
Time Spent

06/23/2020
Last Updated

Explanation





The Golgi tendon organs (GTOs) are sensory receptors located at the junction of the muscle and tendon that are innervated by group Ib sensory axons. GTOs are connected in series with the contracting extrafusal skeletal muscle fibers. When a muscle actively contracts against resistance, the increase in tension is transmitted through the tendon activating the GTOs in the process. In contrast, GTOs are relatively insensitive to changes in muscle length because the lengthening that occurs when a muscle is passively stretched takes place primarily in the muscle fibers and not in the tendon.

The Ib sensory axons from the GTOs contact inhibitory interneurons in the spinal cord, which in turn synapse with the α motor neurons that innervate the same muscle. Thus, the Golgi tendon circuit is a negative feedback system that regulates and maintains muscle tension. When a muscle exerts too much force, the GTOs inhibit contraction of the muscle, causing sudden muscle relaxation. This prevents damage to the

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(Choice A) A-delta fibers are thin, myelinated nerve fibers whose free nerve endings detect temperature and nociceptive stimuli. They are associated with acute (sharp) pain and constitute the afferent portion of the reflex arc that mediates withdrawal from noxious stimuli (e.g., retracting the hand away from a hot stove).

(Choice C) In contrast to the in-series arrangement of GTOs, muscle spindles (intrafusal muscle fibers) are connected in parallel with extrafusal fibers. They are innervated by group Ia and group II sensory axons and are sensitive to changes in muscle length. Muscle spindles mediate the stretch reflex (myotatic reflex), which is commonly tested (deep tendon reflexes) during the neurologic examination. When a muscle is stretched, there is monosynaptic reflex activation of the α motor neuron (of the same muscle), causing contraction that resists the stretch.

(Choices D and E) Pacinian corpuscles are *rapidly* adapting mechanoreceptors located in the subcutaneous tissue of the skin as well as the mesentery, peritoneum, and joint capsules. Ruffini's end organs are *slowly* adapting mechanoreceptors that exist in the skin, subcutaneous tissue, and joint capsule. Both help to mediate touch, proprioception, and vibratory sensation and are innervated by myelinated A-beta fibers.

Educational objective:
The muscle spindle system is a feedback system that monitors and maintains muscle length, while the Golgi tendon system is a feedback system that monitors and maintains muscle force. GTOs are exquisitely sensitive to increases in muscle tension but are relatively insensitive to passive stretch.

References

- The Golgi tendon organ: a review and update

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Physiology	Rheumatology/Orthopedics & Sports	Muscle structure & physiology
Subject	System	Topic

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A 17-year-old boy is referred to a clinic for ongoing muscle weakness. He has noticed difficulty climbing stairs at home over the last several months, and he recently stopped playing basketball due to difficulty lifting the ball over his head. The patient takes no medications and does not know of any family members with muscle weakness. On neurologic examination, he is unable to lift his arms or legs against resistance when fully outstretched. He undergoes a muscle biopsy to evaluate the cause of his proximal muscle weakness. Electron microscopy of the specimen reveals sparse transverse tubules in some of the muscle fibers. Which of the following is the most likely consequence of this patient's biopsy findings?

A. Decremental force generation on repeated muscle stimulation

B. Impaired ATP production during active muscle contraction

C. Impaired relaxation after sustained muscle contraction

D. No contraction of the myocyte in response to increased intracellular Ca^{2+}

E. Uncoordinated contraction of myofibrils within affected muscle fibers

Submit

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A. Decremental force generation on repeated muscle stimulation (13%)

B. Impaired ATP production during active muscle contraction (8%)

C. Impaired relaxation after sustained muscle contraction (3%)

D. No contraction of the myocyte in response to increased intracellular Ca^{2+} (21%)

✓ E. Uncoordinated contraction of myofibrils within affected muscle fibers (52%)

Omitted
Correct answer
E

52%
Answered correctly

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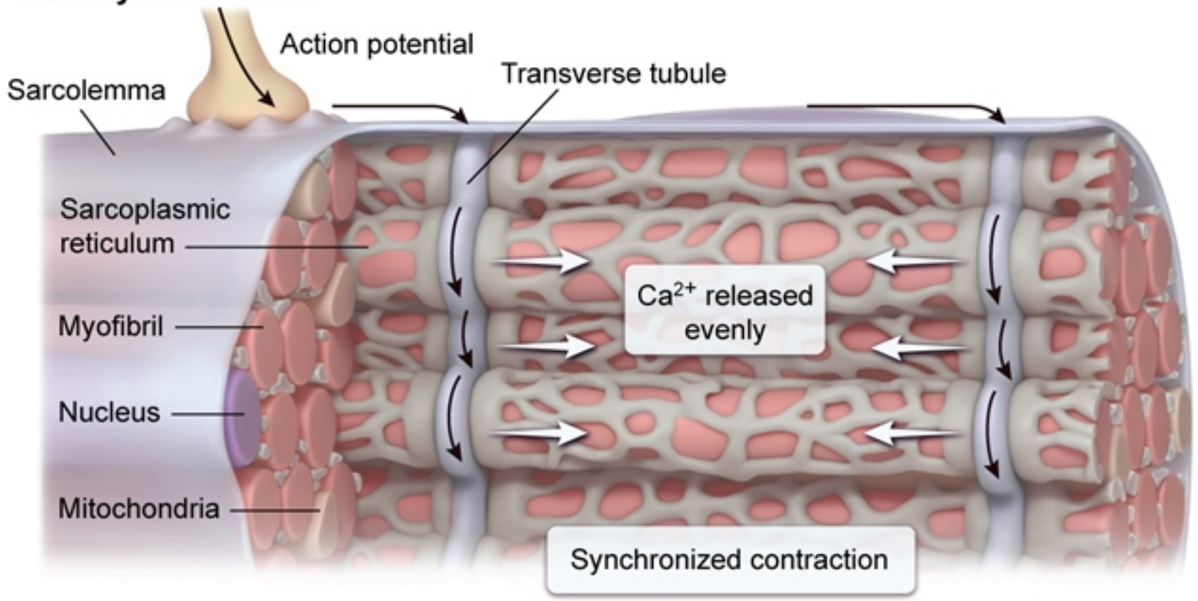
02/22/2020
Last Updated

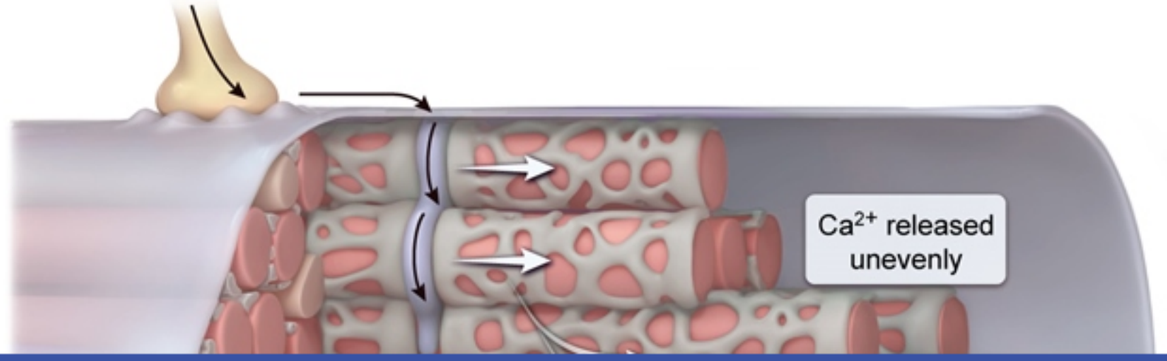
Explanation

Muscle fiber depolarization

Healthy muscle cell



Fewer transverse tubules



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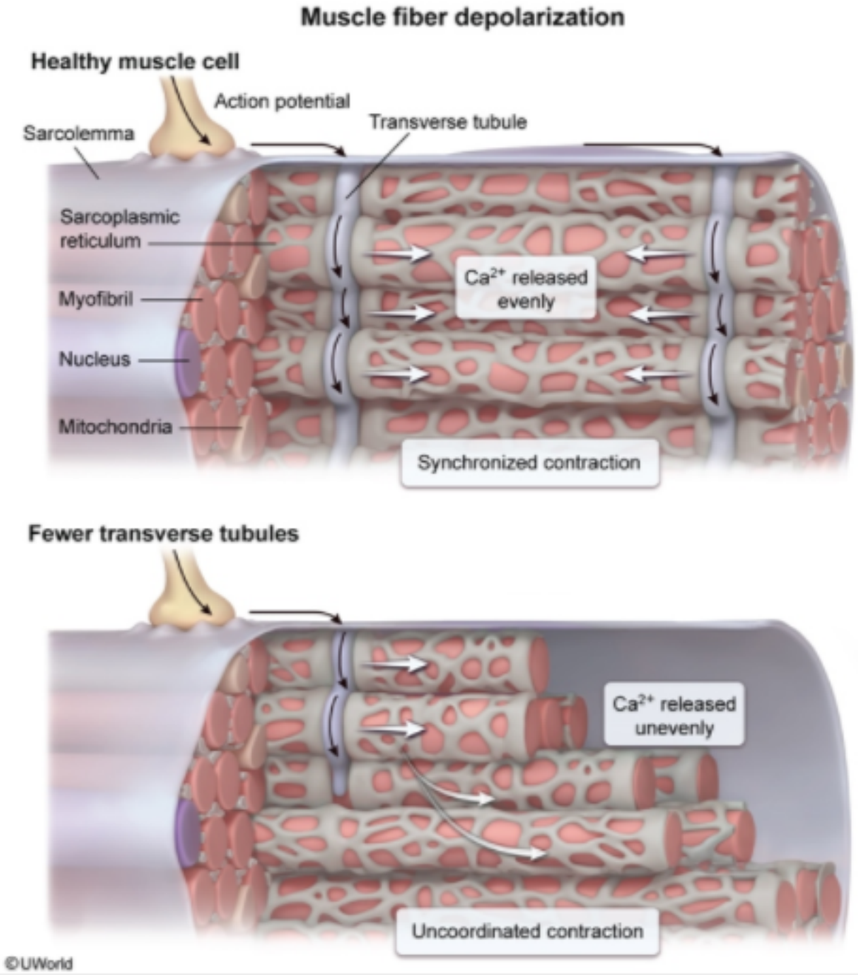

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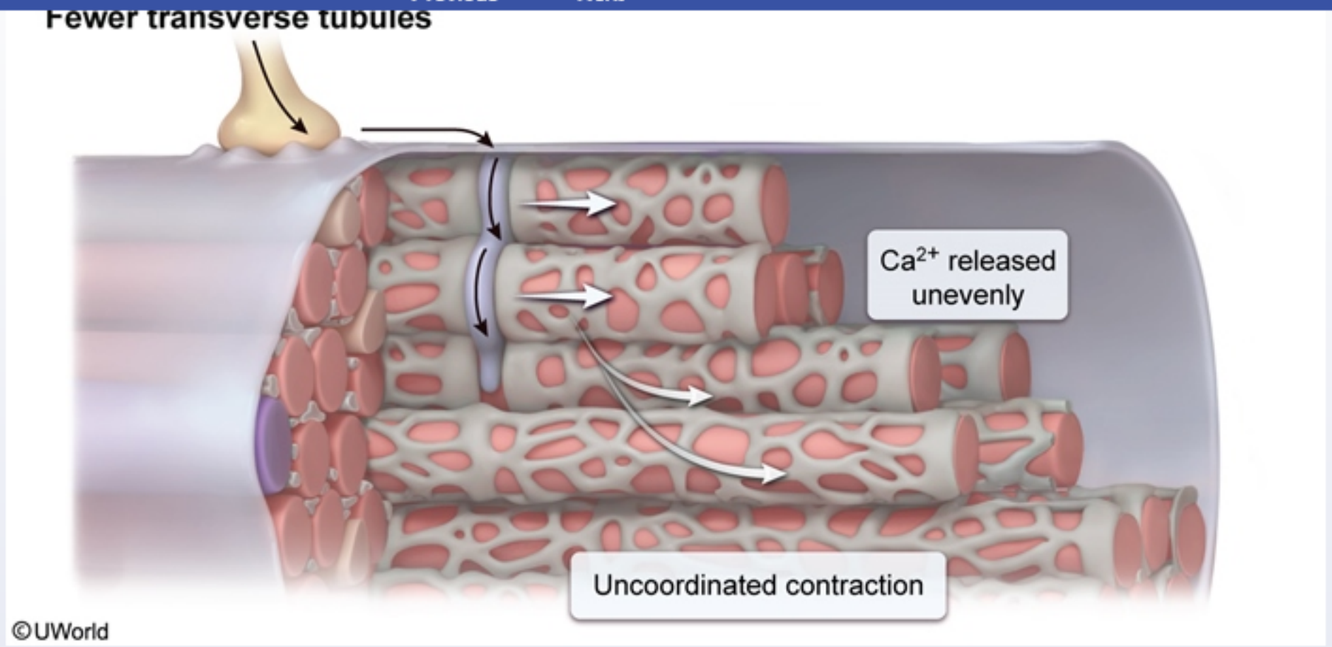

Transverse tubules (T-tubules) are **invaginations** of the muscle cell membrane (**sarcolemma**) located in close proximity to the terminal cisterns of the sarcoplasmic reticulum. They are found in striated (eg, cardiac, skeletal) muscle and contain voltage-gated L-type calcium channels (dihydropyridine receptors) adjacent to the ryanodine receptors on the terminal cisterns. During muscle contraction, T-tubules allow the **depolarization** impulse to **rapidly propagate** through the interior of the muscle fiber. This ensures that calcium release from the sarcoplasmic reticulum occurs uniformly throughout the fiber, allowing for **synchronized contraction of myofibrils** in each muscle cell.

This patient most likely has a form of limb girdle muscular dystrophy due to a mutated sarcolemma protein (eg, caveolin) affecting excitation-contraction coupling. Decreased numbers of functional T-tubules in affected muscle fibers lead to **uncoordinated** contraction of myofibrils, which manifests as muscle weakness.

(Choice A) Decremental force generated on repeated stimulation characterizes myasthenia gravis, an autoantibody disorder inhibiting postsynaptic acetylcholine receptors in the neuromuscular junction. A constant low response to repeated nerve stimulation is more likely if T-tubules are lacking.

(Choice B) ATP fuels myosin movement along actin filaments (causing contraction) and drives the pumps that transport calcium back into the

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(Choice B) ATP fuels myosin movement along actin filaments (causing contraction) and drives the pumps that transport calcium back into the sarcoplasmic reticulum (causing relaxation). McArdle disease is one cause of impaired ATP production and occurs due to a failure of muscle glycogen breakdown.

(Choice C) Impaired relaxation after sustained contraction occurs in myotonic dystrophy due to a trinucleotide repeat expansion altering myotonin-protein kinase. This protein facilitates myosin head detachment from the actin filament to enable muscle relaxation; T-tubules do not play a role.

(Choice D) A mutation in troponin C may block its response to intracellular calcium and prevent muscle contraction. However, muscle fibers with decreased numbers of T-tubules will maintain limited contractility.

Educational objective:
Transverse tubules (T-tubules) are invaginations of the sarcolemma that transmit depolarization signals to the sarcoplasmic reticulum to trigger the release of calcium and induce muscle contraction. The uniform distribution of T-tubules in striated muscle fibers ensures that each myofibril contracts at the same time, which is necessary for efficient contraction.

References

- T-tubule biogenesis and triad formation in skeletal muscle and implication in human diseases.

Physiology	Rheumatology/Orthopedics & Sports	Muscle structure & physiology
Subject	System	Topic

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Exhibit Display

Intracellular calcium regulation

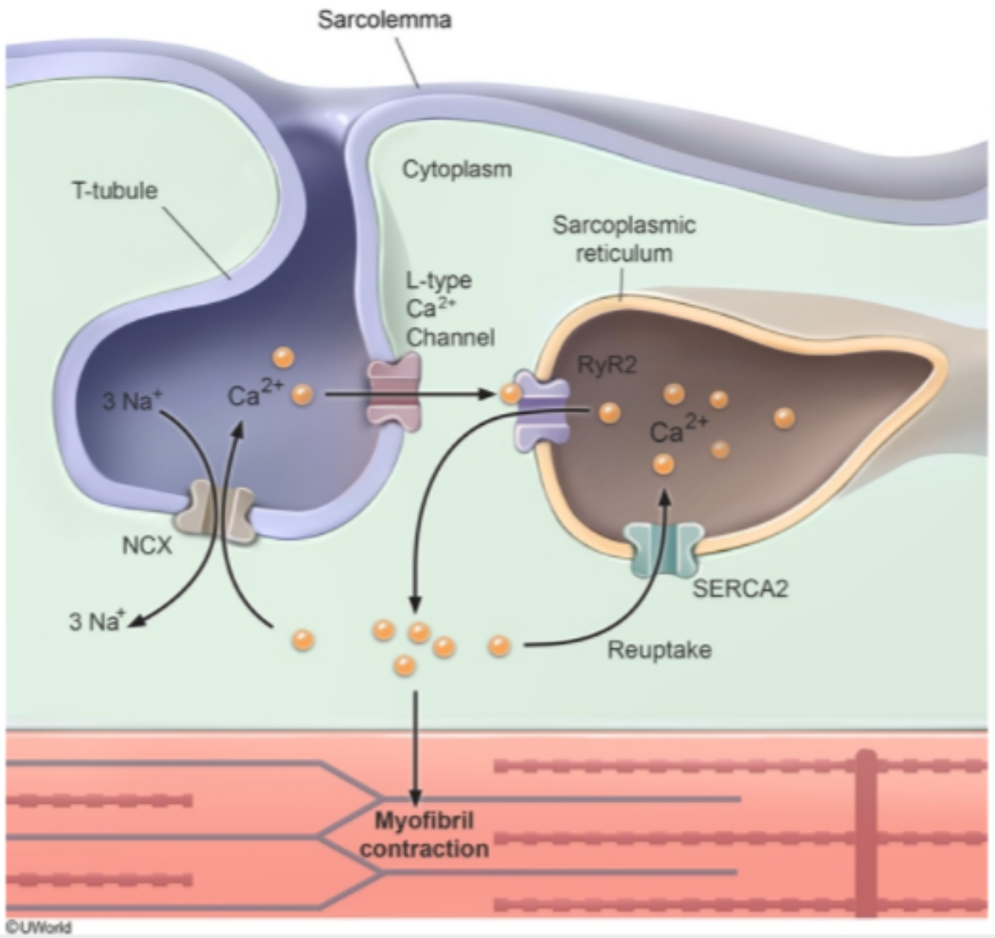

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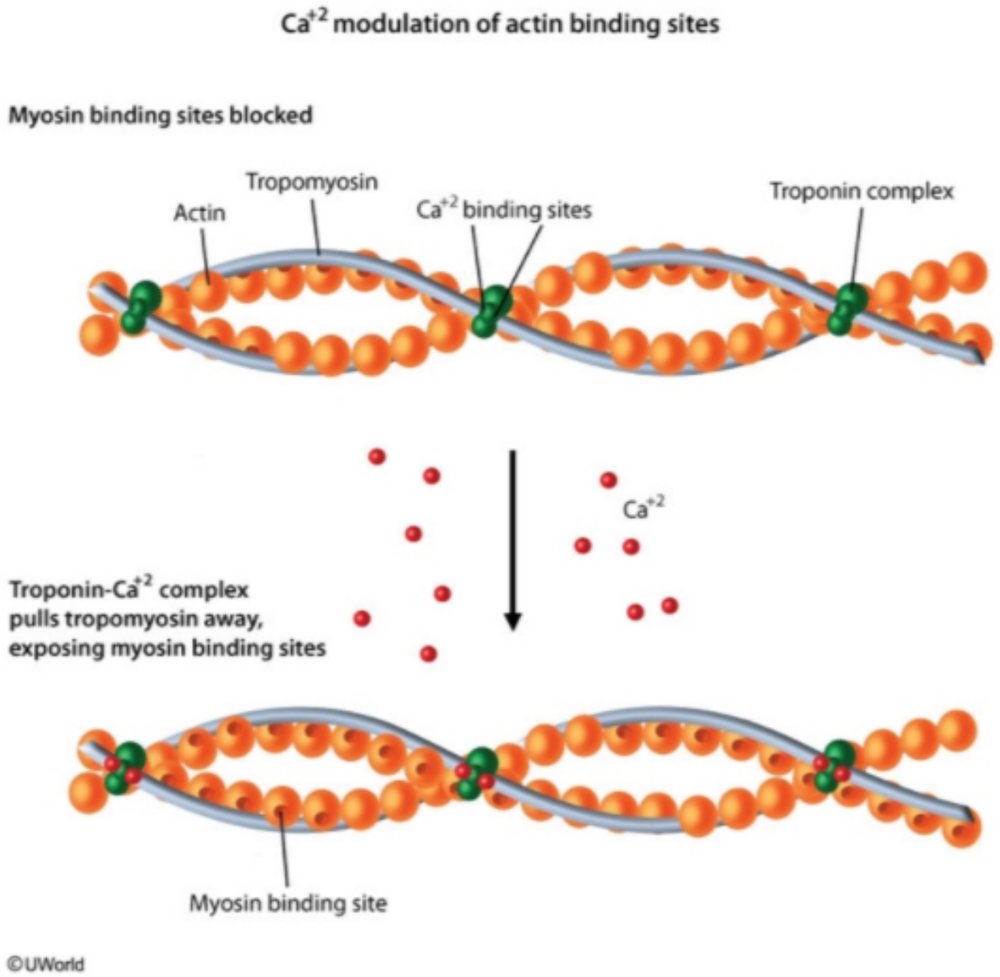
Exhibit Display



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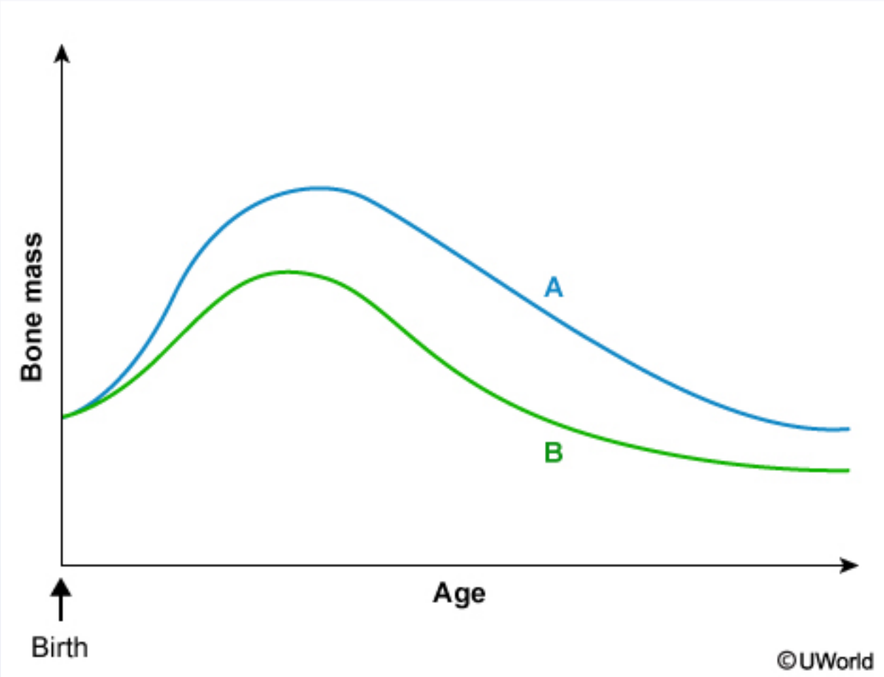
A prospective observational study is performed to determine factors affecting bone mass and fracture risk. Detailed demographic and clinical information is obtained from a large number of volunteers, and bone mass is monitored over time. The data obtained from 2 specific groups of women are shown below.



Which of the following factors is most likely present in group A?

A. Early menopause

B. Increased physical activity

C. Lower body mass index

D. Positive smoking history

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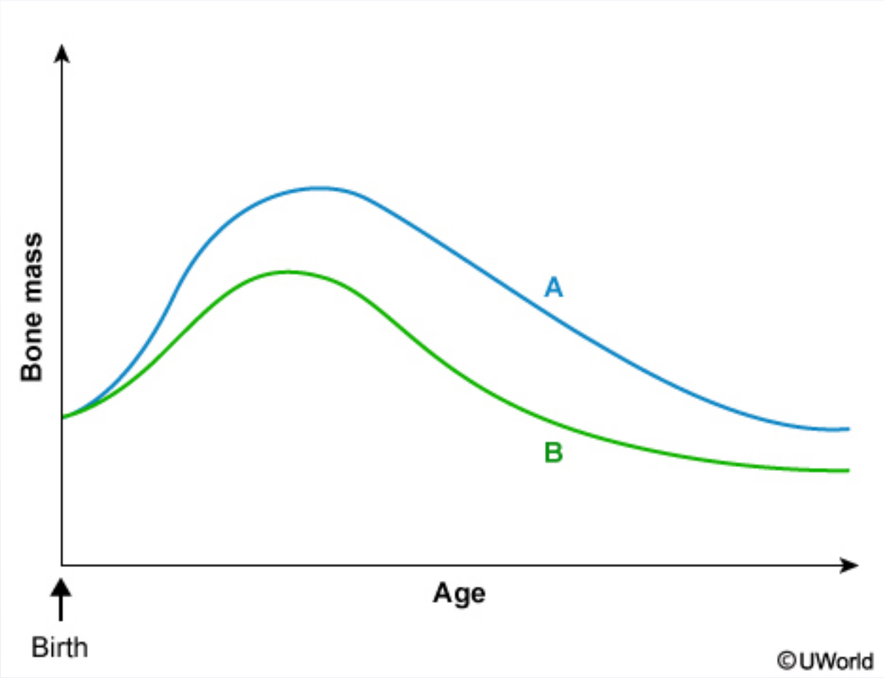

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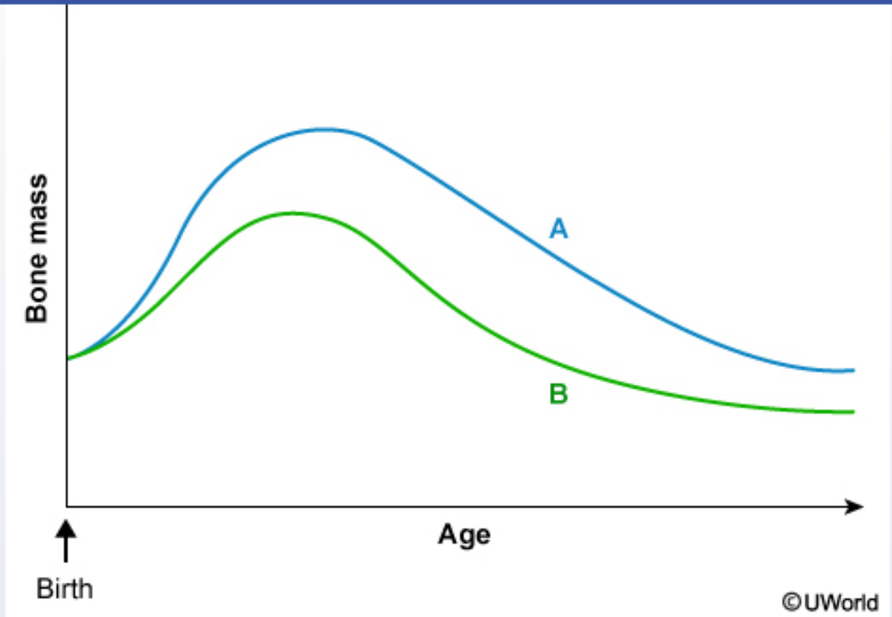
C. Lower body mass index

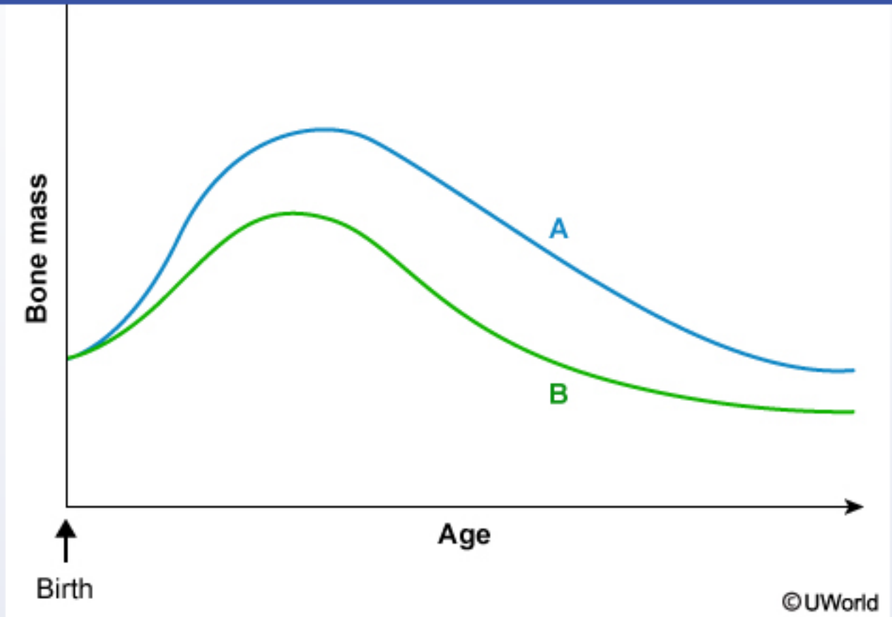
D. Positive smoking history



Which of the following factors is most likely present in group A?

- A. Early menopause
- B. Increased physical activity
- C. Lower body mass index
- D. Positive smoking history
- E. Use of glucocorticoids

Submit



Which of the following factors is most likely present in group A?

- A. Early menopause (1%)
- ✓ B. Increased physical activity (94%)
- C. Lower body mass index (2%)
- D. Positive smoking history (0%)
- E. Use of glucocorticoids (0%)

Omitted
Correct answer

94%
Answered correctly

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03/21/2020
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Risk factors for osteoporotic fractures	
Nonmodifiable	**Potentially modifiable**
• Advancing age • Female sex • White, Hispanic, or Asian ethnicity • Personal or family history of fracture	• Decreased physical activity • Low body weight • Poor calcium & vitamin D intake • Excessive alcohol or tobacco use • Premature menopause • Glucocorticoid use

Bone mass in adulthood is determined by **peak bone mass** and the subsequent rate of **bone loss**. Most of the variation in peak bone mass is genetically determined, but environmental factors such as nutritional status (eg, calcium and vitamin D intake) and physical activity also have a significant impact. Establishment of a high peak bone mass during early adulthood is important because bone mass subsequently declines with age. By convention, **osteoporosis** is defined as a bone density that is 2.5 or more standard deviations below the mean (T score ≤ -2.5) for peak young adult bone density.

The subjects in group A show a higher peak bone mass, slightly lower rate of post-peak bone loss, and higher late-life bone mass than the subjects in group B. This is consistent with the effects of regular **exercise**, especially weight-bearing exercise. In contrast, factors that lead to a lower peak bone mass include genetic and ethnic factors (eg, Asian or Caucasian ethnicity), chronic inflammatory disease, exposure to glucocorticoid medications, and sedentary lifestyle. In addition, prolonged caloric deficits (often seen with excessive exercise) can lead to functional hypothalamic amenorrhea, suppression of estrogen production, and rapid bone loss.

(Choice A) Estrogens have an anabolic effect on bone by increasing osteoblastic activity and decreasing osteoclastic activity. Loss of estrogen effect (eg, menopause, premature ovarian failure) causes accelerated bone loss.

(Choice C) Bone density is proportional to BMI. BMI <22 kg/m^2 (or weight <57.6 kg [127 lb]) is associated with increased risk for osteoporosis.

(Choice D) Smoking causes accelerated bone loss and is a major risk factor for osteoporosis and osteoporotic fractures.

(Choice E) Chronic glucocorticoid use is a major risk factor for osteoporosis. Glucocorticoids decrease the gastrointestinal absorption of calcium

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(Choice E) Chronic glucocorticoid use is a major risk factor for osteoporosis. Glucocorticoids decrease the gastrointestinal absorption of calcium, inhibit collagen synthesis by osteoblasts, decrease GnRH (leading to hypogonadism), and increase urinary calcium loss.

Educational objective:
Regular exercise leads to increased peak bone mass, a reduced rate of bone loss, and a decreased risk of osteoporosis.

References

- Exercise for preventing and treating osteoporosis in postmenopausal women.

Physiology	Rheumatology/Orthopedics & Sports	Osteoporosis
Subject	System	Topic

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An 18-year-old man, who was recently started on risperidone therapy for schizophrenia, comes to the office due to involuntary deviation of his head. On examination, the patient's head is tilted toward the right side and the chin is rotated to the left. There is palpable tightening of the right sternocleidomastoid muscle. It is determined that the patient is experiencing a medication-induced dystonic reaction due to motor neuron hyperactivity. The persistent myocyte stimulation causes a substance to be released from the sarcoplasmic reticulum. This substance most likely binds to which of the following proteins to cause this patient's symptoms?

A. Actin

B. Myosin

C. Tropomyosin

D. Troponin

E. Protein kinase A

Submit

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A. Actin (2%)
B. Myosin (4%)
C. Tropomyosin (17%)
✓ D. Troponin (73%)
E. Protein kinase A (1%)

Omitted
Correct answer
D

73%
Answered correctly

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Time Spent

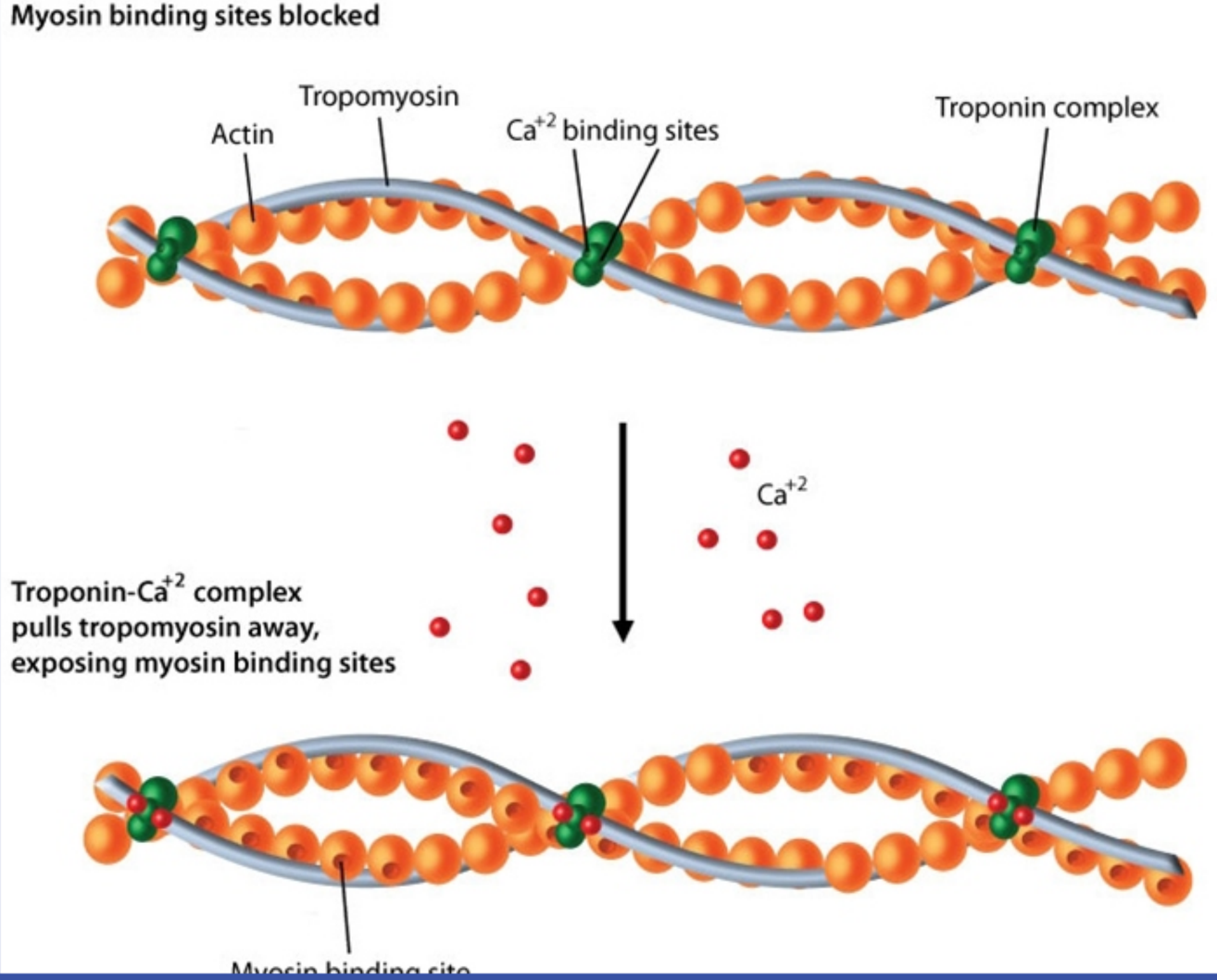
01/11/2020
Last Updated

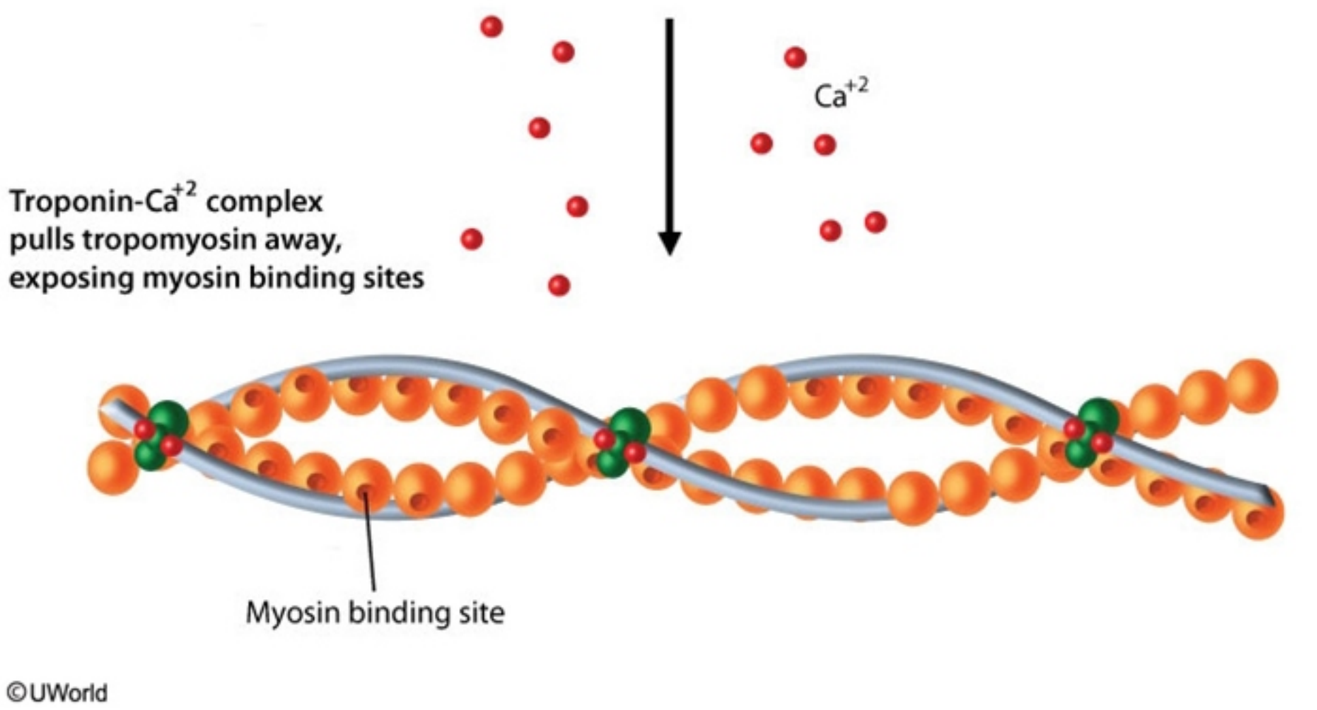
Explanation

Ca^{+2} modulation of actin binding sites

Myosin binding sites blocked

Ca^{+2} modulation of actin binding sites





The **sarcoplasmic reticulum** (SR) is a modified endoplasmic reticulum within skeletal muscle cells. The SR forms a network of tubules with terminal cisterns that are in close contact with the T tubules (cytoplasmic membrane invaginations), allowing the membrane depolarization signal to reach the SR. The **Ca^{2+}-ATPase pump** in the SR membrane actively sequesters calcium to keep intracellular concentrations low. Cell membrane depolarization causes **calcium release** from the SR into the cytoplasm via the SR **ryanodine receptor**.

Actin filaments, troponin complex (troponins C, T, and I), and tropomyosin form the thin filaments of muscle fibers. In the resting state, tropomyosin covers the **myosin binding sites** on the actin filaments. On release from the SR, **calcium** binds to troponin C on the thin filaments **(Choices A and C)**. This induces a conformation change in the troponin complex, causing it to displace tropomyosin and expose the myosin binding sites on the actin filaments.

Myosin makes up the thick filaments of skeletal muscle. ATP is bound by the myosin head and cleaved to form ADP and inorganic phosphate ion

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Myosin makes up the thick filaments of skeletal muscle. ATP is bound by the myosin head and cleaved to form ADP and inorganic phosphate ion, which are retained at the myosin head. When the myosin head binds to an actin filament, a conformational change causes the myosin to pull the actin filament, leading to muscle contraction and ADP release. A new ATP molecule then is bound to the myosin head, causing release of the actin filament. The cycle then repeats until calcium is displaced from troponin C and the myosin binding sites are again covered **(Choice B)**. The pulse of elevated intracellular calcium lasts only a fraction of a second before the calcium is resequestered within the SR.

(Choice E) Protein kinase A is activated by high intracellular concentrations of cAMP and is involved in the second messenger pathways of numerous hormones, including glucagon, beta adrenergic receptors, parathyroid hormone and others.

Educational objective:
During skeletal muscle contraction, calcium is released from the sarcoplasmic reticulum and binds troponin C, thereby allowing the binding of actin to myosin.

References

- Troponin: regulatory function and disorders.

Physiology	Rheumatology/Orthopedics & Sports	Muscle structure & physiology
Subject	System	Topic

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As part of an experiment, radiolabeled ATP is injected into skeletal muscle. During muscle contraction, the labeled ATP is observed to attach to the sarcomere. This attachment causes immediate:

A. Calcium binding to troponin C

B. Tropomyosin displacement from the groove on the actin molecule

C. Myosin head detachment from the actin filament

D. Cross-bridge formation

E. Myosin light chain phosphorylation by a specific enzyme

Submit

As part of an experiment, radiolabeled ATP is injected into skeletal muscle. During muscle contraction, the labeled ATP is observed to attach to the sarcomere. This attachment causes immediate:

A. Calcium binding to troponin C (7%)

B. Tropomyosin displacement from the groove on the actin molecule (7%)

✓ C. Myosin head detachment from the actin filament (70%)

D. Cross-bridge formation (9%)

E. Myosin light chain phosphorylation by a specific enzyme (4%)

Omitted
Correct answer
C

70%
Answered correctly

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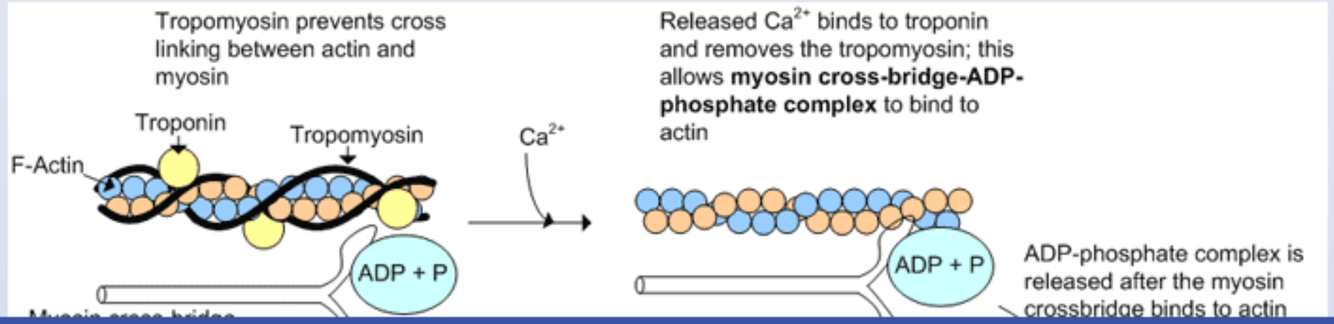
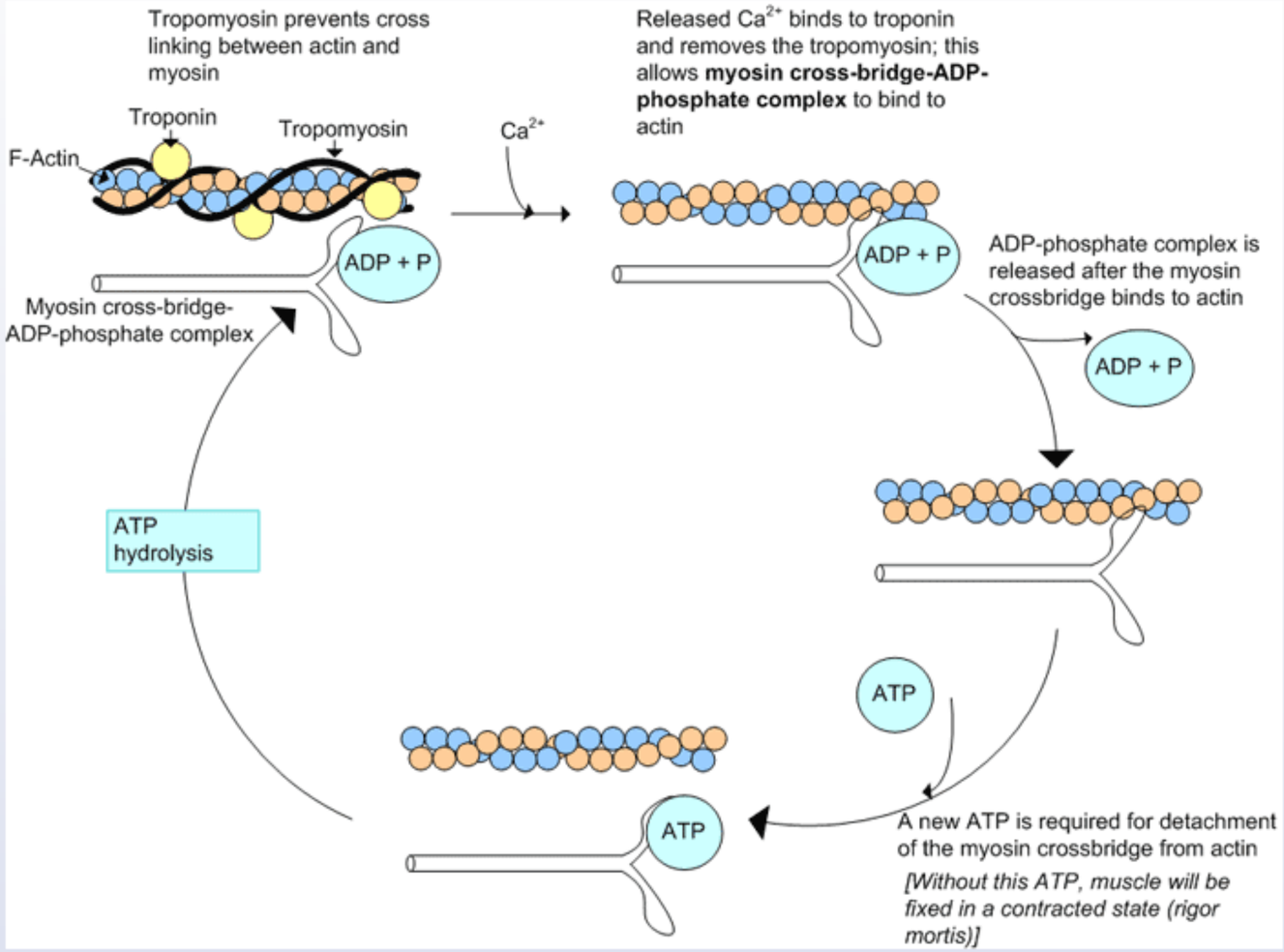
Time Spent

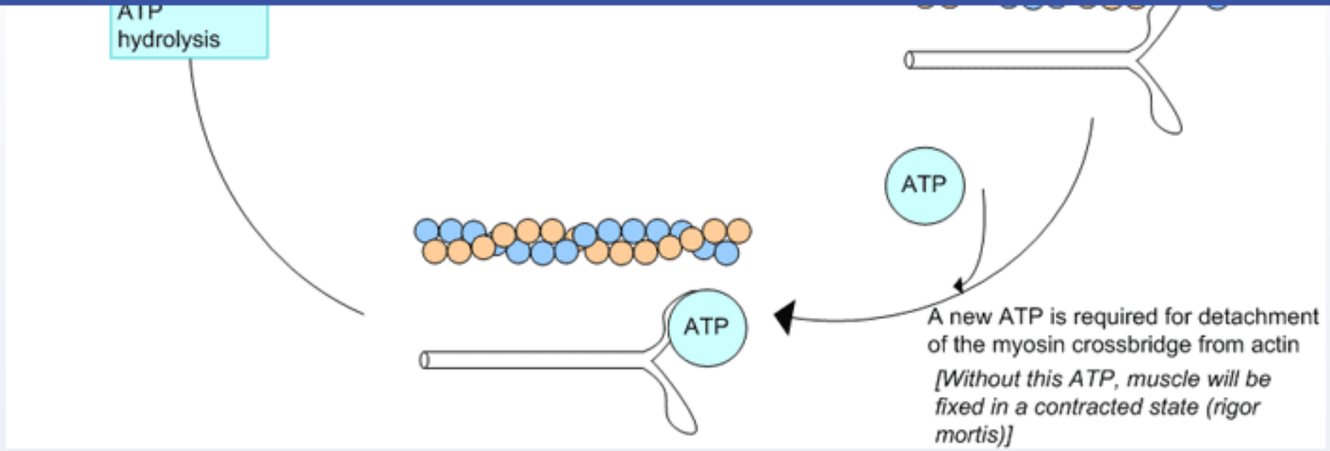
02/03/2020
Last Updated

Explanation





According to the model posited by Rayment et al., the role of ATP in skeletal and cardiac muscle contraction may be to release the myosin head from its actin binding site and then to energize a conformational change that resets the myosin head to "contract" again the next time it binds to actin.



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(Choices A and B) Calcium binding to troponin C shifts tropomyosin away from the myosin binding site on actin. These steps do not depend directly on ATP.

(Choice D) If ATP is not available, the cross-bridge between myosin and actin will persist (rigor mortis).

(Choice E) Myosin light chain kinase phosphorylates the myosin light chain, activating myosin to bind actin filaments in *smooth muscle* cells. There is no myosin head phosphorylation by a specific kinase in skeletal muscle contraction.

Educational Objective:
During the skeletal muscle contraction cycle, ATP binding to myosin causes release of the myosin head from its binding site on the actin filament.

Physiology	Rheumatology/Orthopedics & Sports	Muscle structure & physiology
Subject	System	Topic

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A muscle biopsy obtained from a healthy volunteer consists mainly of myoglobin-rich, glycogen-poor fibers with many mitochondria. Which of the following is the most likely biopsy site?

A. Biceps brachii

B. Deltoid

C. Latissimus dorsi

D. Paraspinal

E. Pectoralis major

Submit

A muscle biopsy obtained from a healthy volunteer consists mainly of myoglobin-rich, glycogen-poor fibers with many mitochondria. Which of the following is the most likely biopsy site?

A. Biceps brachii (15%)
B. Deltoid (2%)
C. Latissimus dorsi (9%)
✓ D. Paraspinal (70%)
E. Pectoralis major (2%)

Omitted
Correct answer
D

70%
Answered correctly

02 secs
Time Spent

07/01/2020
Last Updated

Explanation

Muscle fiber characteristics		
	Type I (slow twitch)	**Type II (fast twitch)**
Action	Sustained force (eg, posture)	Rapid bursts (eg, heavy weightlifting)
Activity type	Endurance (aerobic)	Resistance (anaerobic)
Force generated	Low	High

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	Type I (slow twitch)	**Type II (fast twitch)**
Action	Sustained force (eg, posture)	Rapid bursts (eg, heavy weightlifting)
Activity type	Endurance (aerobic)	Resistance (anaerobic)
Force generated	Low	High
Resistance to fatigue	High	Low
Lipid content	High	Low
Glycogen content	Low	High
Mitochondrial content	High	Low
Energy metabolism	Oxidative	Glycolytic
Color	Red (high myoglobin)	Pale red/white (low myoglobin)
Prototype	Soleus	Triceps

The body's muscles are composed of 2 main fiber types: slow twitch (Type I) and fast twitch (Type II). **Type I fibers** perform actions requiring **low-level sustained force** (eg, postural maintenance) and function primarily via **aerobic metabolism**, meaning they have **high myoglobin** (oxygen storage) and **mitochondrial** (aerobic respiration) concentrations. The soleus muscle of the lower leg and paraspinal muscles of the back are postural muscles predominantly composed of Type I fibers.

Type II fibers are specialized for generating **rapid forceful** movements and they **fatigue quickly**. These fibers derive ATP energy mainly via glycogenolysis and subsequent **anaerobic glycolysis**. Muscles that maneuver the upper extremities **(Choices A, B, C, and E)** are primarily geared toward rapid forceful movements and are more likely to have a higher percentage of Type II than Type I muscle fibers.

Educational objective:

Lipid content	High	Low
Glycogen content	Low	High
Mitochondrial content	High	Low
Energy metabolism	Oxidative	Glycolytic
Color	Red (high myoglobin)	Pale red/white (low myoglobin)
Prototype	Soleus	Triceps

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Educational objective:
Postural skeletal muscles such as the soleus and paraspinal muscles contain predominantly Type I, slow twitch muscle fibers that derive ATP primarily via oxidative (aerobic) metabolism.

References

- Exercise-induced skeletal muscle remodeling and metabolic adaptation: redox signaling and role of autophagy.

Physiology	Rheumatology/Orthopedics & Sports	Muscle structure & physiology
Subject	System	Topic

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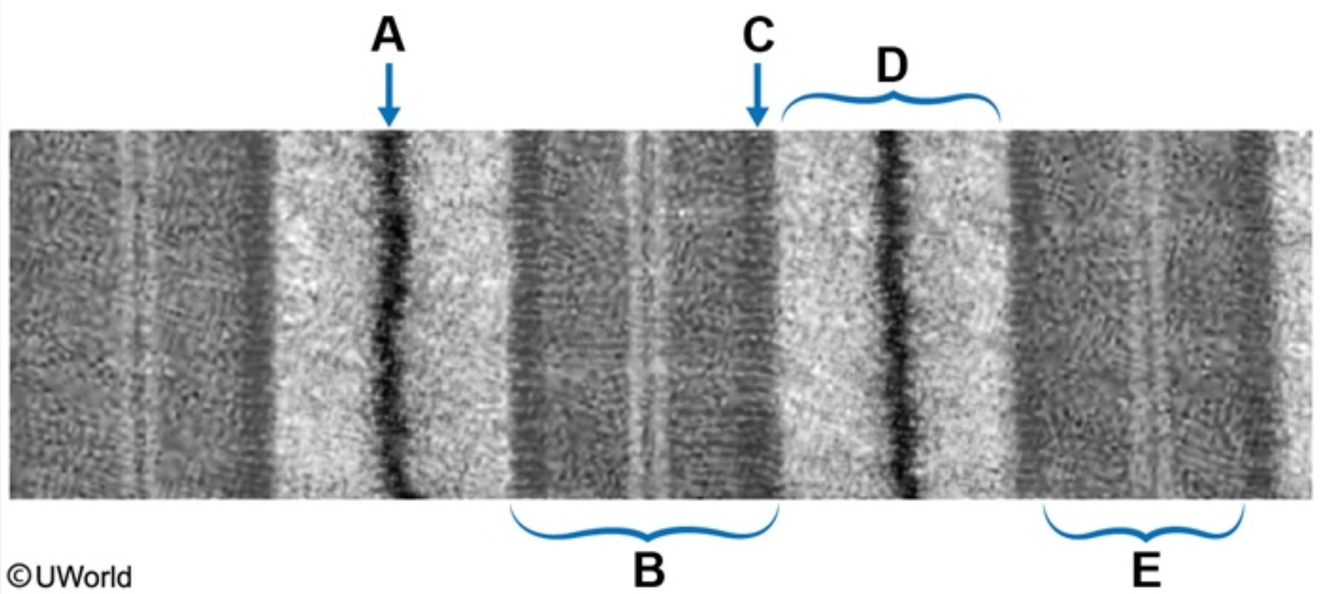
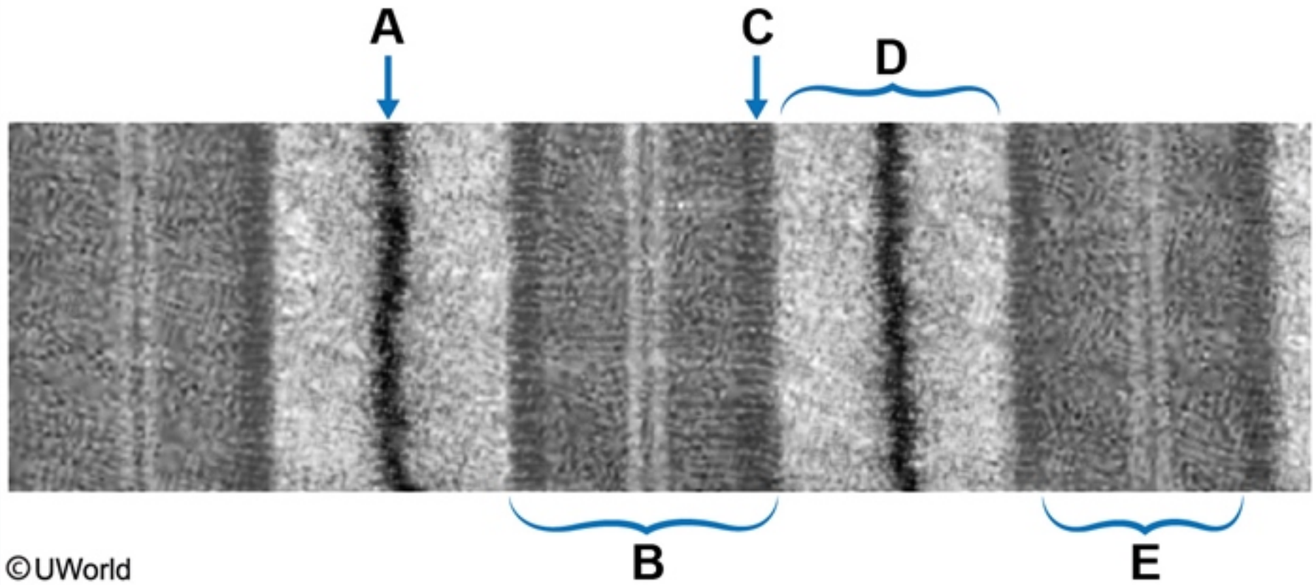
An 8-year-old boy is evaluated in the office due to difficulty walking. The patient has problems running, jumping, and walking up steps. There is no history of neurological disorders in the family. Physical examination reveals weakness of lower extremity muscles bilaterally. Electron microscopy of a biopsy sample taken from calf muscle is shown below.



Which of the following labeled regions contains only thick filaments and no thin filaments?

- A. A
- B. B
- C. C
- D. D
- E. E



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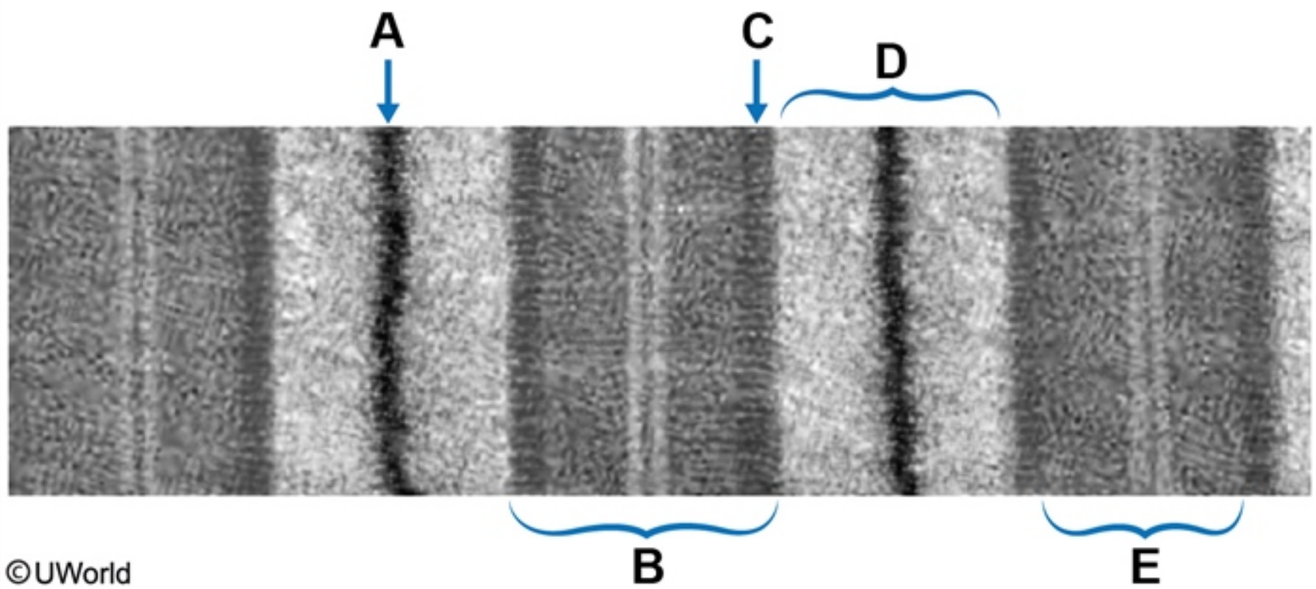
- C. C
- D. D
- E. E

Submit



Which of the following labeled regions contains only thick filaments and no thin filaments?

- A. A (10%)
- B. B (10%)
- C. C (8%)
- D. D (10%)
- ✓ E. E (61%)

Omitted
Correct answer

61%
Answered correctly

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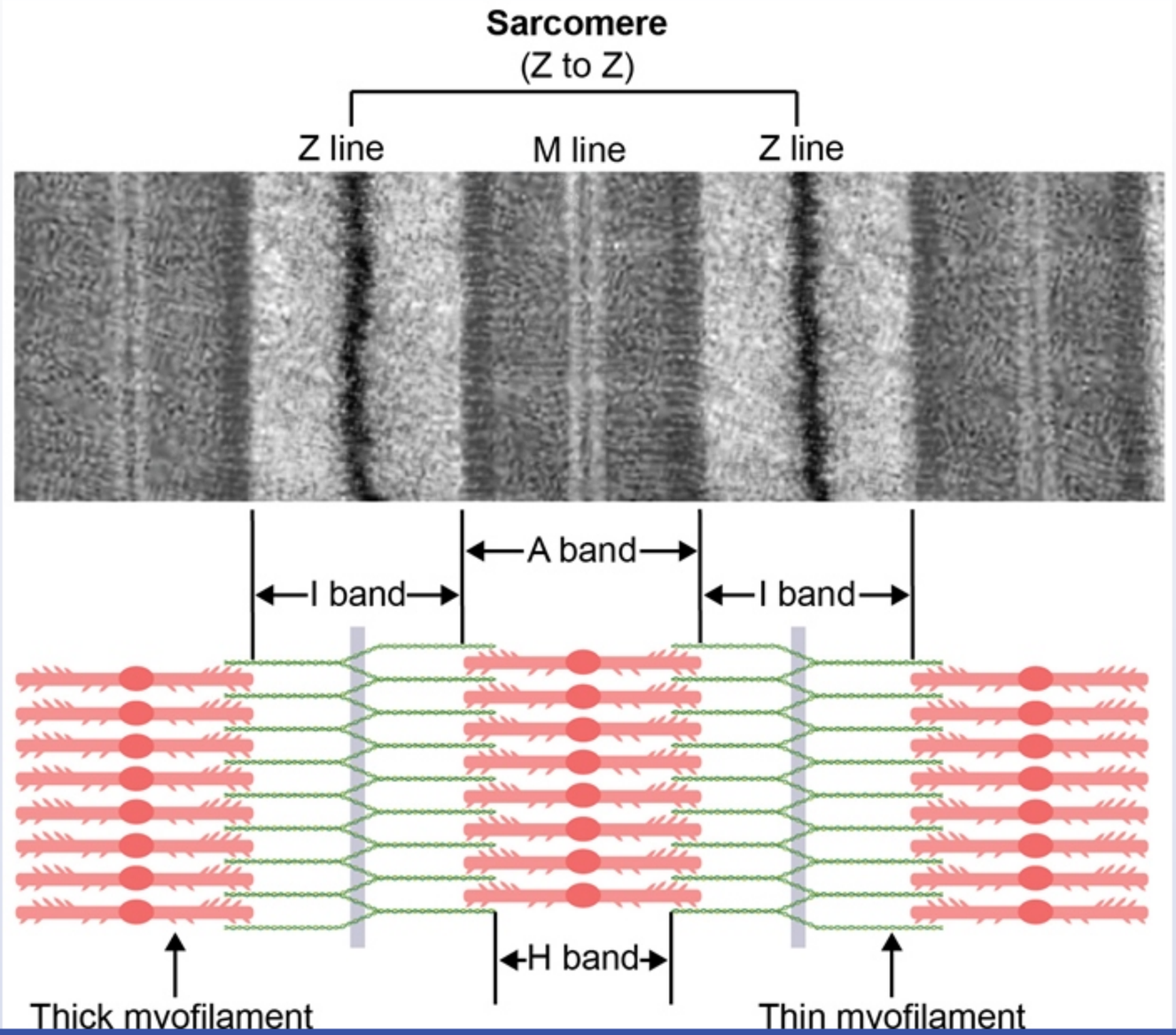
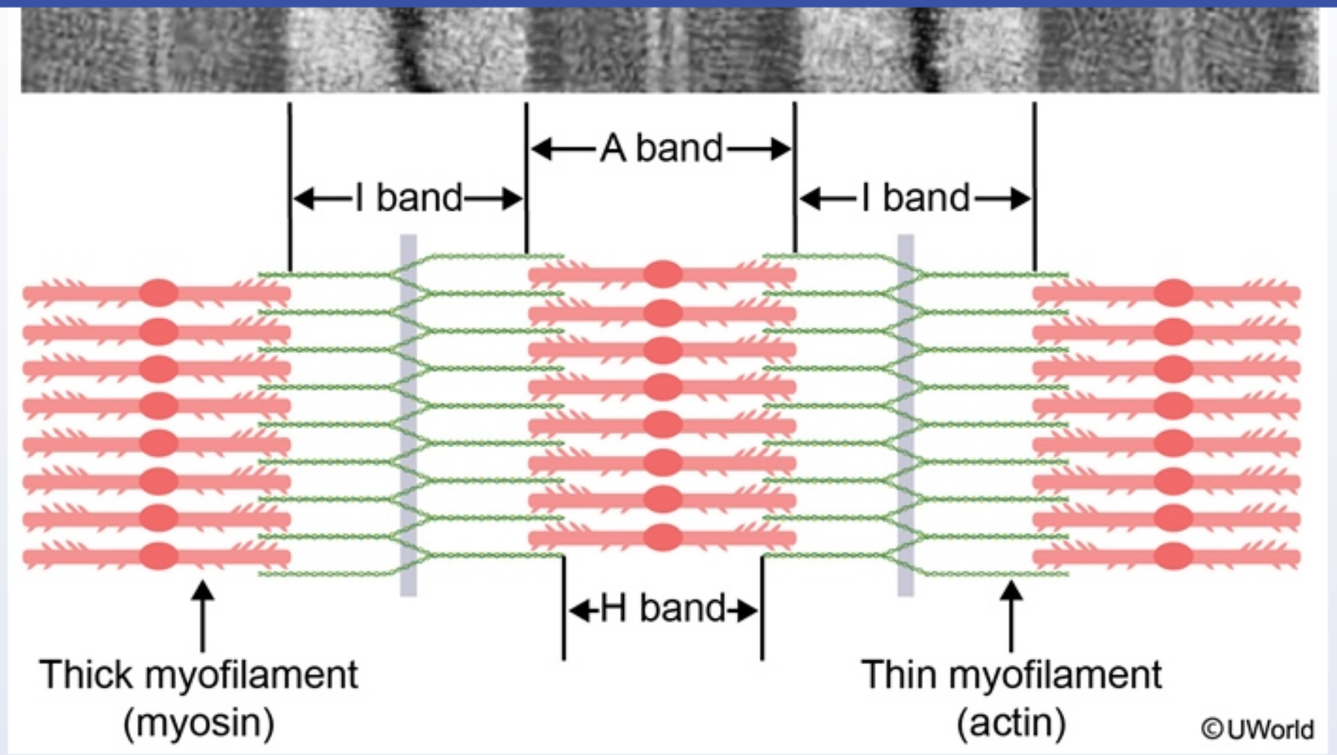
Time Spent

03/09/2020
Last Updated


Sarcomere
(Z to Z)
Z line
M line
Z line
A band
I band
I band
H band
Thick myofilament
Thin myofilament

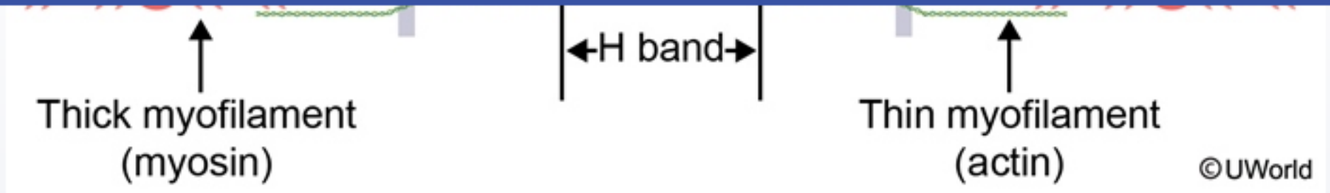


The **H band** is the region of the sarcomere containing only **thick (myosin) filaments**. On electron microscopy, the H band is a portion of the A band that **straddles the M line**. The A band corresponds to the thick filaments in the sarcomere and includes portions overlapped by thin (actin) filaments **(Choice B)**. During muscle contraction, the thin filaments slide over the thick filaments toward the M line, reducing the length of the H band. The A band always remains the same length.

(Choice A) The Z line is typically distinctly darker than the remainder of the sarcomere. Thin filaments, which are composed of actin, tropomyosin, and troponin, anchor at the Z line.

(Choice C) The segment of the sarcomere between the H and I bands is where thick and thin filaments overlap.

(Choice D) The I band contains the Z line and only those sections of the thin filaments that do not overlap with thick filaments. During muscle contraction, both the I band and H band decrease in length.



The **H band** is the region of the sarcomere containing only **thick (myosin) filaments**. On electron microscopy, the H band is a portion of the A band that **straddles the M line**. The A band corresponds to the thick filaments in the sarcomere and includes portions overlapped by thin (actin) filaments **(Choice B)**. During muscle contraction, the thin filaments slide over the thick filaments toward the M line, reducing the length of the H band. The A band always remains the same length.

(Choice A) The Z line is typically distinctly darker than the remainder of the sarcomere. Thin filaments, which are composed of actin, tropomyosin, and troponin, anchor at the Z line.

(Choice C) The segment of the sarcomere between the H and I bands is where thick and thin filaments overlap.

(Choice D) The I band contains the Z line and only those sections of the thin filaments that do not overlap with thick filaments. During muscle contraction, both the I band and H band decrease in length.

Educational objective:
The H band is the region of the sarcomere that contains only thick (myosin) filaments. The H band is the part of the A band (which is on either side of the M line) where thick filaments have no overlapping thin (actin) filaments.

References

- The muscle ultrastructure: a structural perspective of the sarcomere.
- The sarcomeric cytoskeleton: from molecules to motion.

Physiology	Rheumatology/Orthopedics & Sports	Muscle structure & physiology
Subject	System	Topic

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The resting membrane potential for an isolated muscle cell is -70 mV. Equilibrium potentials for important ions are given below:

E_{Na} = + 60 mV
E_K = - 80 mV
E_{Cl} = - 70 mV
E_{Ca} = + 125 mV

Which of the following most likely forms the resting membrane potential of the cell?

A. High potassium conductance and some sodium conductance
B. High chloride conductance and some sodium conductance
C. High calcium conductance and some chloride conductance
D. High potassium conductance and some chloride conductance
E. High potassium conductance only

Submit

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E_{K} = - 80 mV
E_{Cl} = - 70 mV
E_{Ca} = + 125 mV

Which of the following most likely forms the resting membrane potential of the cell?

- A. High potassium conductance and some sodium conductance (54%)
- B. High chloride conductance and some sodium conductance (4%)
- C. High calcium conductance and some chloride conductance (3%)
- D. High potassium conductance and some chloride conductance (14%)
- E. High potassium conductance only (22%)

Omitted
Correct answer
A

54%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

The resting potential refers to the difference in charge across the cell membrane at rest (when there is no signaling activity). The membrane prevents the free diffusion of ions, and generally there is an excess of positive ions outside the cell and an excess of negative ions in the

The resting potential refers to the difference in charge across the cell membrane at rest (when there is no signaling activity). The membrane prevents the free diffusion of ions, and generally there is an excess of positive ions outside the cell and an excess of negative ions in the cytoplasm. This separation of positive and negative charges across the cell membrane gives rise to an electrical potential difference that ranges from -60 to -80 mV; the typical resting membrane potential of a cell is -70 mV.

The cytoplasm of a typical cell is characterized by a low concentration of Na and high concentration of K. The extracellular fluid is inversely rich in Na and low in K. This difference in Na and K concentration is maintained by the Na,K-ATPase, which pumps three Na ions out of the cell for every 2 K ions allowed into the cell.

Every charged ion that the cell membrane is permeable attempts to push the resting membrane potential of the cell toward its equilibrium potential. The resting membrane potential can therefore be viewed as a combination of the equilibrium potentials of the ions that can penetrate the cell membrane. Each permeable ion does not contribute equally to the membrane potential; it is obvious that the resting membrane potential does not equal the average of the different equilibrium potentials. The greater the permeability of a given ion, the greater its contribution to the resting membrane potential will be. Ions with little permeability will contribute very little to the resting membrane potential. In the resting cell the permeability of the membrane for K is much higher than that for Na. Outflow of K ions through non-gated channels maintains the negative charge inside the membrane, which approaches the equilibrium potential for K. There are, however, a small number of channels that allow the flow of Na into the cell. This small influx of Na ions decreases the membrane potential, and for this reason the resting potential of the membrane is always less negative than the equilibrium potential for K **(Choice A)**.

(Choice B) If the chloride equilibrium potential is -70 mV and the resting membrane potential is -70 mV, then chloride would need to be the only membrane permeable ion with no contribution from other ions. Chloride, in reality, plays little role in the determination of the membrane potential.

(Choice C) High calcium conductance would make the resting membrane potential positive, and the question stem states that the membrane potential is -70 mV.

(Choice D) High potassium conductance does occur at rest and is the largest contributor to the resting membrane potential. Chloride plays little to no role in the determination of the resting membrane potential.

(Choice E) If a high potassium conductance were the only contributor to the resting membrane potential, then the membrane potential would be the same as the potassium equilibrium potential.

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(Choice D) High potassium conductance does occur at rest and is the largest contributor to the resting membrane potential. Chloride plays little to no role in the determination of the resting membrane potential.

(Choice E) If a high potassium conductance were the only contributor to the resting membrane potential, then the membrane potential would be the same as the potassium equilibrium potential.

Educational Objective:
The resting membrane potential is the difference in the electrical charges across the cell membrane under steady-state conditions. The ions that are most permeable to the cell membrane make the largest contribution to the resting membrane potential. In general, a high potassium efflux and some sodium influx are responsible for the value of the resting potential, which is typically about -70 mV.

Physiology	Rheumatology/Orthopedics & Sports	Resting membrane potential and action potential
Subject	System	Topic

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Molecular biologists perform a series of experiments to characterize the electrophysiologic properties of human muscle cells. The resting membrane potential for an isolated muscle cell is determined to be -70 mV. The equilibrium potentials for important ions under normal physiologic conditions are as follows:

E_{Na} = + 60 mV
E_{K} = - 90 mV
E_{Cl} = - 75 mV
E_{Ca} = + 125 mV
E_{Mg} = 0 mV

If physiologic conditions are maintained, which of the following ions would most likely flow out of the cell after opening of their respective ion channels?

A. Magnesium and calcium
B. Magnesium and chloride
C. Potassium and chloride
D. Potassium only
E. Sodium and calcium

Submit

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E_{Na} = + 60 mV
E_{K} = - 90 mV
E_{Cl} = - 75 mV
E_{Ca} = + 125 mV
E_{Mg} = 0 mV

If physiologic conditions are maintained, which of the following ions would most likely flow out of the cell after opening of their respective ion channels?

A. Magnesium and calcium (1%)
B. Magnesium and chloride (1%)
C. Potassium and chloride (42%)
✓ D. Potassium only (42%)
E. Sodium and calcium (12%)

Omitted
Correct answer
D

42%
Answered correctly

02 secs
Time Spent

04/29/2020
Last Updated

Explanation

Equilibration movements of charged ions under physiologic conditions

Ion	Charge	Major location	Equilibrium potential	Equilibration movement at -70 mV
Sodium	Positive	Extracellular	+ 60 mV	Extracellular gradient drives Na^+ into cell, making membrane potential more positive **(Choice E)**
Potassium	Positive	Intracellular	- 90 mV	Intracellular gradient drives K^+ out of cell, making membrane potential more negative
Chloride	Negative	Extracellular	- 75 mV	Extracellular gradient drives Cl^- into cell, making membrane potential more negative **(Choices B and C)**
Calcium	Positive	Extracellular	+ 125 mV	Extracellular gradient drives Ca^{2+} into cell, making membrane potential more positive **(Choice A)**

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Na^+, K^+, and Cl^- are the main ions that determine the electrical potential difference (voltage) across a membrane (**membrane potential**). Under normal physiologic conditions, there is a low concentration of Na^+ and Cl^- in the cell and high concentration of K^+ in the cytoplasm. Conversely, the

Calcium	Positive	Extracellular	+ 125 mV	making membrane potential more positive **(Choice A)**

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Na^+, K^+, and Cl^- are the main ions that determine the electrical potential difference (voltage) across a membrane (**membrane potential**). Under normal physiologic conditions, there is a low concentration of Na^+ and Cl^- in the cell and high concentration of K^+ in the cytoplasm. Conversely, the extracellular space has a high concentration of Na^+ and Cl^- ions and low concentration of K^+ ions.

Because intracellular K^+ concentration is much greater than its extracellular concentration, opening of cellular potassium channels leads to K^+ efflux from the cell along the K^+ concentration gradient. Within the cell, the positive charge of the K^+ ions is normally neutralized by the negative charge of intracellular anions (eg, phosphates and proteins) that are trapped in the cell. As K^+ ions leave the cell, negatively charged anions accumulate along the inner side of the cell membrane. This continually increasing negative charge attracts the positively charged K^+ ions back into the cell. When the difference in concentration (diffusion potential) of K^+ inside and outside the cell is large, the efflux of K^+ ions will continue despite the increasing negative charge. At a certain point, however, the negative intracellular charge (electrical potential) of the membrane becomes large enough that the number of K^+ ions it attracts into the cell equals the number of K^+ ions that leave the cell along the concentration gradient. The electrical potential difference that moves K^+ ions into the cell at the same rate as they leave the cell along the concentration gradient is called the **equilibrium potential**.

Educational objective:
When a specific ion channel opens, the respective ions will flow across the membrane in a direction that brings the resting membrane potential closer to that ion's equilibrium potential.

References

- Generation of resting membrane potential.

Physiology	Rheumatology/Orthopedics & Sports	Resting membrane potential and action potential
Subject	System	Topic

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A 16-year-old boy comes to the office for an annual health maintenance visit. He has no medical conditions and feels well. The patient plays football for his high school team and states he is planning to increase his physical workouts to prepare for the upcoming season. He indicates that last season he was often fatigued during the second half of games, and he plans to focus on endurance training. Physical examination shows no abnormalities. Which of the following is most likely to increase in this patient's large skeletal muscle groups after a prolonged period of regular training?

A. Anaerobic glycolytic enzymes

B. Mitochondrial content

C. Number of motor endplates per fiber

D. Proportion of type II (fast-twitch) fibers

E. Total quantity of myocytes

Submit

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A. Anaerobic glycolytic enzymes (12%)
✓ B. Mitochondrial content (73%)
C. Number of motor endplates per fiber (2%)
D. Proportion of type II (fast-twitch) fibers (7%)
E. Total quantity of myocytes (4%)

Omitted
Correct answer
B

73%
Answered correctly

02 secs
Time Spent

07/03/2020
Last Updated

Explanation

Muscle fiber characteristics		
	Type I (slow twitch)	Type II (fast twitch)
Action	Sustained force (eg, posture)	Rapid bursts (eg, heavy weightlifting)

Muscle fiber characteristics		
	Type I (slow twitch)	**Type II (fast twitch)**
Action	Sustained force (eg, posture)	Rapid bursts (eg, heavy weightlifting)
Activity type	Endurance (aerobic)	Resistance (anaerobic)
Force generated	Low	High
Resistance to fatigue	High	Low
Lipid content	High	Low
Glycogen content	Low	High
Mitochondrial content	High	Low
Energy metabolism	Oxidative	Glycolytic
Color	Red (high myoglobin)	Pale red/white (low myoglobin)
Prototype	Soleus	Triceps

Skeletal muscle fibers (or myocytes) are categorized into 2 major types based on the magnitude and sustainability of contraction force they generate and their predominant method of energy production.

Type I fibers (slow-twitch fibers) specialize in **stamina** (fatigue resistance) but can generate only relatively **low force** per contraction. These fibers primarily use **oxidative phosphorylation** (OP) to allow for sustained and efficient production of ATP. Therefore, they have a **high content** of **lipids** (fatty acids are a primary energy source for OP), **myoglobin** (to supply oxygen), and **mitochondria** (the cellular location of OP). The high myoglobin content gives these fibers a red color.

Type II fibers (fast-twitch fibers) primarily specialize in rapid bursts of strength; they generate **high force** per contraction but **quickly fatigue**. These fibers produce ATP primarily via **anaerobic glycolysis** and have **high glycogen** levels. Therefore, they have low quantities of mitochondria and myoglobin (giving them a pale red or white color).

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Targeted physical training stimulates specific phenotypic adaptations in skeletal muscle fibers to improve skeletal muscle function. **Endurance training** (eg, distance running, sustained light-to-moderate weightlifting) **promotes** the characteristics of **type I fibers** (eg, increased size and quantity of mitochondria) and also increases capillary density. In contrast, resistance training (eg, heavy weightlifting) amplifies the characteristics of type II fibers while also stimulating increased muscle mass.

(Choice A) Anaerobic glycolytic enzymes will decrease and aerobic oxidative enzymes will increase with endurance training.

(Choice C) Muscle fibers are arranged into a motor unit, with each unit innervated by a single motor neuron and endplate. Although the size and metabolic characteristics of muscle fibers change with training, the number of muscle fibers within a motor unit or endplates per fiber does not change.

(Choices D and E) Endurance training amplifies the phenotypic characteristics of existing type I fibers; however, the total quantity of muscle fibers (myocytes) or the proportion of each type of muscle fiber does not change with training.

Educational objective:
Type I muscle fibers (slow-twitch or red fibers) primarily use oxidative phosphorylation and contain high quantities of lipids, myoglobin, and mitochondria. They specialize in sustained, low force contraction, and their function is amplified by endurance training. Type II muscle fibers (fast-twitch or white fibers) primarily use glycolysis and specialize in rapid bursts of high force contraction. Their function is amplified by resistance training.

References

Type II fibers (fast-twitch fibers) primarily specialize in rapid bursts of strength; they generate **high force** per contraction but **quickly fatigue**. These fibers produce ATP primarily via **anaerobic glycolysis** and have **high glycogen** levels. Therefore, they have low quantities of mitochondria and myoglobin (giving them a pale red or white color).

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References

- Exercise-induced skeletal muscle remodeling and metabolic adaptation: redox signaling and role of autophagy.

Physiology	Rheumatology/Orthopedics & Sports	Physical exercise
Subject	System	Topic

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